Report of the

IPWSO
International
Prader-Willi Syndrome
Organisation

Mental Health Network

Improving mental health and well-being for people with Prader-Willi syndrome

an IPWSO special initiative

www.ipwso.org

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Abbreviations

ACC	Anterior Cingulate Cortex
ACTH	Adrenocorticotrophic Hormone
ADHD	Attention Deficit Hyperactivity Disorder
ADOS	Autism Diagnostic Observation Schedule
AgRP	Agouti-Related Protein
AGRP	Agouti-Related Peptide
ANS	Autonomic Nervous System
APARDO	Asia Pacific Alliance of Rare Diseases Organisations
ASC	Autistic Spectrum Condition(s)
BIRD	Baschirotto Institute for Rare Disorders
BMI	Body Mass Index
CART	Cocaine- and Amphetamine-Regulated Transcript
CBCL	Child Behaviour Checklist
CCK	Cholecystokinin
CNS	Central Nervous System
CNVs	Copy Number Variants
CRH	Corticotrophin-Releasing Hormone
CYFIP1	Cytoplasmic FMR1 Interacting Protein 1
DBC	Developmental Behaviour Checklist
DCCR	Diazoxide Choline Controlled Release
DC-LD	Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disability/Mental Retardation
DM-ID	Diagnostic Manual – Intellectual Disability
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECHO	Extension for Community Healthcare Outcomes (from Project ECHO)
EF	Executive Functions
ERCAL	Enfermedades Raras en el Caribe y América Latina
ERPs	Event-Related Potentials
FDA	Food and Drug Administration (USA)
FPWR	Foundation for Prader-Willi Research
FraX	Fragile X Syndrome
GABA	Gamma-Aminobutyric Acid
GCP5	Gamma-Tubulin Complex Component 5
GHT	Growth Hormone Treatment
GLP-1	Glucagon-Like Peptide-1
GWAS	Genome-Wide Association Studies
GXR	Guanfacine Extended Release
HGP	Human Genome Project
HPA	Hypothalamic-Pituitary-Adrenal (axis)
HQCT	Hyperphagia Questionnaire for Clinical Trials
HRQoL	Health-Related Quality of Life

Abbreviations

IC	Imprinting Centre
ICD	Imprinting Centre Defect
ICD	International Classification of Diseases
IDD	Intellectual Developmental Disability
IMHN	IPWSO Mental Health Network
IPWSO	International Prader-Willi Syndrome Organisation
IQ	Intelligence Quotient
MAGEL2	MAGE Family Member L2
MKRN3	Makorin Ring Finger Protein 3
mUPD	Maternal Uniparental Disomy
NDN	Necdin
NHS	National Health Service (UK)
NIPA1/ NIPA2	Non-imprinted in Prader-Willi/Angelman Syndrome 1 & 2
NORD	National Organization for Rare Disorders
NPY	Neuropeptide Y
OCD	Obsessive-Compulsive Disorder
PADQ	PWS Anxiousness and Distress Behaviours Questionnaire
PFC	Prefrontal Cortex
POMC	Pro-Opiomelanocortin
PTSD	Post-Traumatic Stress Disorder
PVN	Paraventricular Nucleus
PWRFA	Prader-Willi Research Foundation of Australia
PWS	Prader-Willi Syndrome
PYY	Peptide YY
RDI	Rare Diseases International
RDoC	Research Domain Criteria
SA	Suicide Attempt
SI	Suicidal Ideation
SNORD116	Small Nucleolar RNA, C/D Box 116
SNURF-SNRPN	SNURF-SNRPN Gene Complex (small nuclear ribonucleoproteins)
SSRI	Selective Serotonin Reuptake Inhibitor
UEB3A	Ubiquitin Protein Ligase E3A
UHC	Universal Health Coverage
UN CRPD	United Nations Convention on the Rights of Persons with Disabilities
UPD	Uniparental Disomy
VYKAT™ XR	Commercial name for DCCR (extended-release formulation)
WHO	World Health Organization
YBOCS	Yale-Brown Obsessive Compulsive Scale

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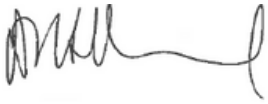

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The membership of the IPWSO Mental Health Network was global, with representatives from 22 countries. These included parents as well as psychiatric, psychological and behavioural experts, together with other clinicians and health and social care professionals, all experts in the support of people with PWS. The names and affiliations of the IMHN Members who contributed to this initiative are listed below.

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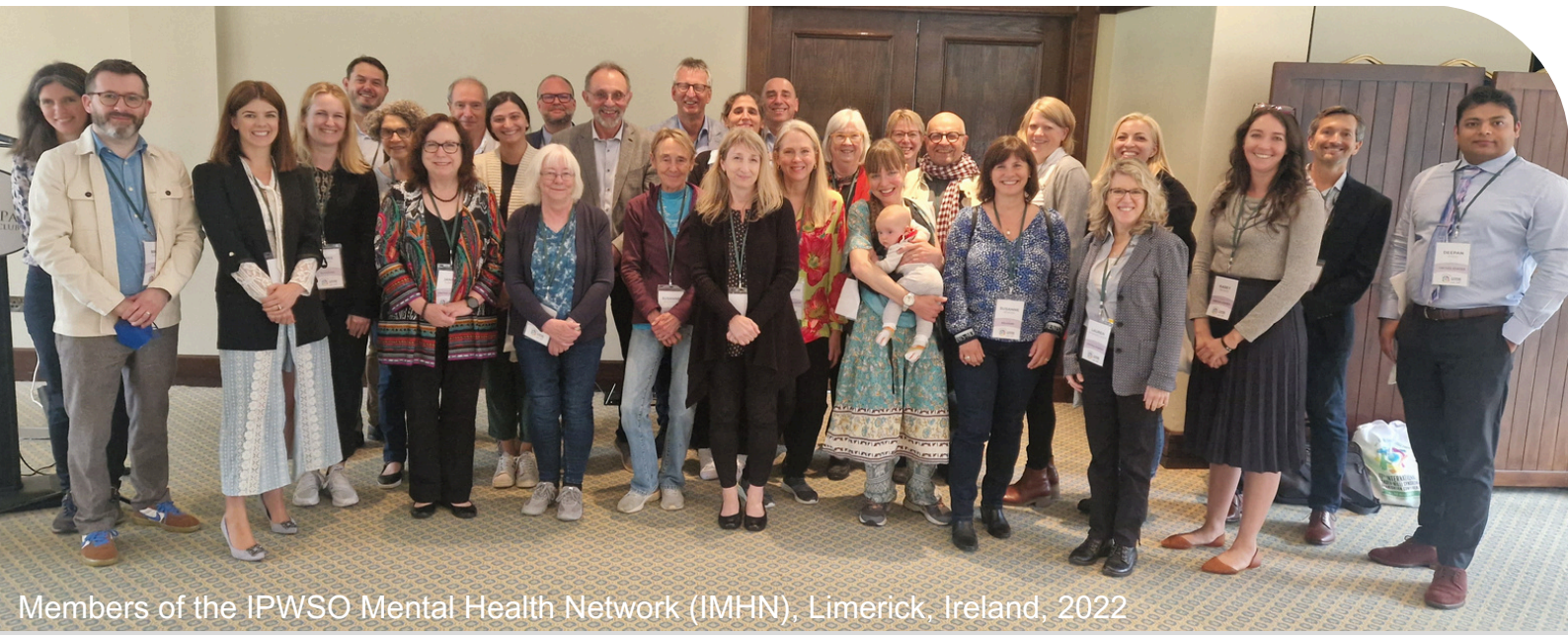

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Summary

PART 1
Alongside their complex physical health and social needs, individuals with Prader-Willi syndrome (PWS) face elevated risks of mental ill health and the occurrence of particular behaviours of concern that are characteristic of PWS. Given the global shortage of specialist expertise and the lack of consensus on assessment and treatment, the International Prader-Willi Syndrome Organisation (IPWSO) established a multidisciplinary Mental Health Network. This group, comprising parents, psychiatrists, psychologists, professional social care providers, allied health professionals, and behavioural experts, aimed to build a shared understanding of the behavioural and mental health needs of children and adults with PWS, explore underlying causes, and develop effective prevention and treatment strategies.

Early in the process, parents proposed that a perspective focused solely on the behavioural and mental health issues of their children was insufficient. They emphasised the need to extend our considerations to encompass concepts such as well-being and quality of life.

The Network reviewed research, shared global experiences, and collaborated through virtual meetings and an in-person workshop. Adults with PWS contributed their lived experience, shaping the content and recommendations, which are included throughout this Report. Drawing on collective insights and expert review, this document presents the Network's key findings and guidance for improving behavioural and mental health outcomes in people with PWS. Based on the content of the Report, academic papers will be prepared and submitted for publication and made available through IPWSO.

PART 2
To ensure clarity across clinical and cultural contexts, Part 2 defines foundational concepts that underpin assessment and support:

- **Well-being** is viewed through subjective, objective, and values-based lenses, using a nested model encompassing emotional, physical, psychological, environmental, and personal dimensions.

- **Quality of life** expands on well-being, incorporating economic status, human rights, and social inclusion. Health-related quality of life (HRQoL) integrates physical, mental, and social health.

- **Mental health** is understood as a dynamic state of emotional and social functioning, while **mental ill health** includes cognitive, emotional, and behavioural challenges, whether or not a formal diagnosis is present.

Standard diagnostic frameworks (e.g., DSM, ICD) are seen as problematic when applied to the assessment of people with neurodevelopmental conditions like PWS, underscoring the need for comprehensive, person-centred approaches encompassing the particular complexities associated with the syndrome.

These definitions, and our emerging understanding of their developmental, social and biological determinants, laid the foundation for the work of the group and led to subsequent ideas around holistic and integrated models of care.

PART 3

This section outlines the cognitive, behavioural, and psychiatric characteristics associated with PWS, emphasising the role of both genetic and environmental influences. This cluster is sometimes referred to as the 'behavioural and neuropsychiatric phenotype of PWS'. We use the term 'dimensions of mental ill health' to emphasise that these aspects of the PWS phenotype are rarely all or nothing; rather, each is better understood as a spectrum, varying in severity within a given person with PWS over time and between different individuals with the syndrome.

We separate what we have referred to as 'behaviours of concern' (e.g. hyperphagia, emotional outbursts, skin picking, repetitive and ritualistic behaviours) from those that are primarily characterised by altered mental states (e.g. anxiousness, affective disorders, psychotic illness). These various phenotypic characteristics reflect the fact that PWS is fundamentally a neurodevelopmental condition, characterised by the impact of an atypical pattern of brain development on cognition, functional competence, and the ability to respond to environmental demands.

- **Cognition, communication, and social functioning:** Intellectual and cognitive impairments, impaired cognitive flexibility and task-switching ability, and impaired social cognition are common. The cluster of characteristics diagnostic of autism is more prevalent in those with the maternal uniparental disomy (mUPD) form of PWS.

- **Repetitive and ritualistic behaviours:** Routines, hoarding, perseveration, and repetitive questioning, which are distinct from obsessive compulsive disorder (OCD), may reflect anxiousness and the effects of cognitive rigidity.

- **Hyperphagia:** An inability to limit energy (food) intake in line with the body's energy requirements is characteristic of PWS and is considered to be biologically determined. While the underlying causes for hyperphagia are not fully understood, impaired hypothalamic development, resulting in a small hypothalamus and hypothalamic dysfunction, is implicated. The severity of hyperphagia can vary; however, without some control over access to food, it is likely to lead to life-threatening obesity and associated complications.

- **Emotional outbursts:** Present in 60–70% of people with PWS, are often triggered by minor disruptions or perceived injustices and can significantly impact the well-being of the wider family. The outbursts usually follow a characteristic course, varying in length, and typically resolve with evidence of distress and regret on the part of the person with PWS.

- **Self-harming behaviours:** Skin picking (and, less commonly, rectal picking) is common and occurs to varying degrees in the majority of people with PWS. This behaviour may be exacerbated by stress and under certain environmental conditions, such as the absence of structured activity. Contributing factors may include skin irritation, a high pain threshold, and a need for sensory stimulation.

- **Mental state abnormalities:** People with PWS are often described as anxious, this in general does not meet the criteria for an anxiety disorder and may be better described as anxiousness. These feelings may arise in response to unexpected change, uncertainty, or confusion around food rules and availability. Some individuals exhibit unstable and fluctuating moods, at times resembling features of bipolar disorder. Particularly in those with PWS due to a mUPD, there is an increased risk of developing an affective psychotic illness in the teenage years or early adulthood. Features may include hallucinations (across different sensory modalities), delusions, disorders of thought, and apparent confusion, sometimes with characteristics suggestive of delirium. This atypical psychosis has been likened to descriptions in the literature of cycloid psychosis.

- **Suicidality:** A minority of people with PWS have been reported to experience suicidal thoughts or engage in suicidal behaviours, usually linked to psychiatric disorders, emotional dysregulation, and stress.

This complex neuropsychiatric profile highlights the need for nuanced, multidisciplinary care.

PART 4

Part 4 explores the interwoven biological, psychological, and environmental factors influencing well-being and the dimensions of mental ill health observed in children and adults with PWS:

- **Determinants of well-being and quality of life:** These include the positive effect of general factors, such as good health, a sense of autonomy, and social connectivity. In contrast there are the adverse effects of PWS-specific challenges (hyperphagia, behavioural difficulties). High levels of caregiver burden, financial pressures, and lack of services can further affect quality of life for the person with PWS and their family. While health related factors are important, both well-being and quality of life are also shaped by financial and social resources, access to supported education in childhood, and supported employment, and appropriate, informed social care in adult life.

- **Behaviours of concern and mental ill health:** Atypical brain development and associated cognitive impairments, including those affecting social cognition, create vulnerabilities that may directly result in the development of certain challenging behaviours. Hyperphagia, is considered to result from reduced satiety signalling due to impaired hypothalamic development. Whether or not hyperphagia leads to severe obesity depends on environmental circumstances and the presence (or absence) of food controls and food security.

  The increased propensity for emotional outbursts observed in people with PWS is increasingly understood as a consequence of impaired emotional regulation, potentially due to autonomic nervous system dysfunction. However, the frequency and severity of these behaviours are also shaped by environmental conditions and the previous response of others when they occurred.

Anxiousness is often situational, for example, triggered by unexpected change. It may be associated with a feeling of uncertainty, compounded by difficulties in understanding social context and having the cognitive reserve to be able to respond to change. It is exacerbated when a clear and consistent plan around food is not in place.

Vulnerability to disturbances in affect (mood) may be a consequence of impaired hypothalamic function and its impact on the hypothalamic pituitary axis. The high risk of psychosis in those with the mUPD form of PWS is hypothesised to result from the excess expression of maternally imprinted genes on chromosome 15, which differentiates mUPD from the deletion subtype.

- **Integrated models:** Neurocognitive, behavioural, ecological, and biomedical models often need to be combined to fully capture the complexity of the cognitive, behavioural and neuropsychiatric phenotype of PWS and to guide intervention.

- **Genotype–phenotype links:** The extent to which specific genes on chromosome 15, such as SNORD116, MAGEL2, and Necdin, are directly linked to behaviours of concern or mental ill health continues to be debated. Genetic subtypes (e.g., deletion vs. mUPD) influence psychiatric vulnerability, and the size of the deletion may also have a limited impact.

- I**mplications for practice:** A biopsychosocial framework is essential, recognising the multi-causal nature of behaviours and guiding tailored interventions.

This section sets the stage for Part 5, which focuses on practical assessment and intervention.

PART 5

This section offers practical, evidence-based strategies for promoting mental health and managing behaviours of concern affecting children and adults with PWS:

1. **Promoting well-being and quality of life:** Support must address both shared and PWS-specific needs while tackling systemic barriers that may limit opportunities available to people with PWS. Positive political will, an accepting culture, inclusive social policies, and support, not only from health services, but also from education and the wider care system are crucial. Informed support fills the gap between a person's abilities and the requirements for a more independent life. High levels of parental stress and inadequate services may compound already challenging conditions and may themselves require intervention.

2. **Early Intervention:** While there are limited studies specifically involving people with PWS, a rich literature exists concerning early intervention for people with neurodevelopmental conditions generally. The aims of such intervention for infants and children with PWS include supporting parents to develop the necessary caregiving skills, develop personalised strategies to improve functional and social outcomes, and preparing for the management of hyperphagia when it develops. Research on the use of intranasal oxytocin early in life is on-going, with the hope of improving long-term outcomes. Families need targeted support, particularly during key developmental transitions.

3. **Managing hyperphagia:** As the child grows older, new challenges arise in managing hyperphagia. The primary intervention has been to prevent its consequences, particularly severe obesity, by establishing clear rules around food availability and quantity. This requires careful planning and, for adults, may include shared living with others with PWS and physical security around food.Where such systems are in place, anxiousness often improves and people with PWS may become distressed if rules are broken (e.g. leaving a food cupboard unlocked). It remains uncertain to what extent children with PWS can learn to exert control over their eating behaviour, which could have long-term benefits. Emerging treatments like VYKAT™ XR (DCCR) offer promise, but some level of food control and predictability around food (food security) will likely remain essential. The nature and extent of any controls should be tailored to the individual.

4. **Behaviour management:** A detailed assessment is important to inform the design of interventions. This may include asking family or carers to track behaviours over time. Emotional outbursts and self-harming behaviours require integrated responses, including environmental adjustments, coping plans, psychological support, and, where appropriate, careful medication use. Tools like the PWS Intervention Pyramid provide structured guidance, and assessments based on the principles of applied behavioural analysis can also provide useful insights. All interventions should be evaluated, and particularly in the case of medication (see below), if no benefits are evident, it should be reduced and stopped.

   There were differences in opinion about the use of psychiatric medication for treating behaviours of concern. Case studies of the use of antidepressant, antipsychotic and mood stabilising medications for treating behavioural outbursts have been reported but there have been no properly controlled trials of these medications.

   Findings from a placebo-controlled double-blind trial of guanfacine provided support for the use of such medication to treat behavioural outbursts and other behaviours of concern. The general view, however, is that medication has a limited place in the treatment of emotional outbursts. Given the potential for interventions of different modalities, a treatment plan and process of evaluation is essential as part of good practice.

5. **Mental health treatment:** Psychiatric symptoms must be carefully assessed. Anxiousness is often situational and benefits from ensuring, as far as is possible, predictable routines (timetables), and a clear food management plan. Where there has been a marked and often sudden deterioration in a person's mental state and a diagnosis of a co-morbid psychotic illness is made then the use of antipsychotic medication would be indicated. The choice of medication should be guided by the clinical assessment and where possible avoiding those medications that are known to impact on appetite and lead to weight increase. They should be started at a lower-than-normal dose and increased with care. Whenever they are prescribed they should be used cautiously and alongside non-pharmacological approaches based on individual need at that time.

6. **Service design:** Services should be PWS-informed, accessible, and multidisciplinary, offering early and crisis intervention, respite, and ongoing specialist support. In remote communities, telehealth has the potential to expand service reach.

7. **Transition to adulthood:** Transition planning should be gradual and person-centred, addressing changes in living arrangements, education, employment, and healthcare. A case example illustrates the positive outcomes possible when transitions are well-managed.

Effective support demands flexible, context-aware, and person-centred systems of care.

PART 6

The final section outlines IPWSO's strategic road map to advance understanding, equity, and care for individuals with PWS worldwide:

1. **Global Inequalities:** Access to diagnosis, care, and emerging therapies is inconsistent both within and between countries. Addressing these disparities requires global coordination and better data on cross-cultural care practices.

2. **Family and generational impacts:** Earlier diagnosis and intervention can improve outcomes for younger individuals, but more research is needed to determine whether these benefits are sustained in the longer term. Families remain central to care and need strong, ongoing support.

3. **Scientific integration:** Research must unite genetics, neuroscience, psychology, and social science to fully address the complexity of PWS.

4. **Complex interventions:** Holistic treatment extends beyond medication to include behavioural, psychological, and social approaches. Promising drugs like VYKAT XR raise questions about access and long-term benefit.

5. **R&D Strategy:** IPWSO proposes three strategic pillars:
   - Equity: Understand how context shapes care and work to reduce disparities.
   - Well-being: Identify key well-being drivers and develop adaptable supports.
   - Treatment innovation: Focus on underlying mechanisms, biomarkers, and accessible therapies.

Terms of reference

The Board of Trustees of IPWSO agreed to establish a Mental Health Network in June 2021. The following are the terms of reference agreed by the Board and ratified by the members of the Mental Health Network.

1. To undertake a consultation exercise to consider how well-being, quality of life, and mental health are best characterised with respect to people with PWS and how the factors that affect mental ill health can be most effectively and meaningfully defined, building on the recent work of FPWR in this field.

2. To identify and document the present state of our understanding of the reasons for the complex pattern of problem behaviours and mental-ill health specifically associated with PWS.

3. To develop agreed shared practice guidelines informed by research that aim to optimise personal well-being and quality of life and best enable the prevention, detection, and treatment of mental ill health and problem behaviours.

Part 1: Introduction to the Report

Introduction

1.0.0 IPWSO

1.0.1 The International Prader-Willi Syndrome Organisation (IPWSO) is a charity registered in the UK with global membership. The vision of IPWSO is 'a world where people with Prader-Willi syndrome (PWS) and their families receive the services and support they need to reach their full potential and achieve their goals'.

However, at present there are considerable inequalities globally, with significant differences within and between countries as to when a diagnosis of PWS is made; the extent to which there is access to knowledge and to treatment; and whether or not services and financial support are available to families.

Within mental healthcare there is both very considerable need and very limited expertise and support.

1.1.0 Why is a Mental Health Report needed?

1.1.1 PWS was first described in the scientific literature in 1956 (Prader et al., 1956). It is a rare complex genetically-determined condition, which primarily affects brain development, with secondary impacts on the endocrine and other systems of the body.

Just like anyone else, people with PWS each have their own strengths and characteristics. However, as a group they are at particularly high risk for specific challenging behaviours and for mental ill health. It is these aspects of PWS, together with the broader concepts of quality of life, including personal well-being, that are the focus of this Report.

The Report is written for clinicians, researchers, parents, and others who care for, or are working with, people with PWS.

1.1.2 As we discuss in detail later in the Report, the emergence of over-eating behaviour (hyperphagia) that becomes apparent in early childhood is a central feature of the syndrome, and one that remains a significant challenge throughout the person's lifetime. If access to food is not supervised, and if necessary, restricted, the hyperphagia is very likely to result in life-threatening obesity. In addition to the hyperphagia, there is a greater propensity to emotional outbursts, self-injurious behaviour in the form of skin and rectal picking, and to repetitive and ritualistic behaviours.

Anxiety (referred to as anxiousness in the Report), mood instability and mood disorders, and a high risk of developing an affective psychotic illness in adolescence or early adult life, particularly in those with one genetic type of PWS, are also significant characteristics.

Intellectual and other cognitive impairments are also present to varying degrees. This cluster of characteristics has come to be known as the 'neuropsychiatric' or 'behavioural phenotype' of PWS. It has been shown to significantly impact the quality of life of people with PWS and their families.

1.1.3 Although in many parts of the world there is a lack of clinical expertise, there is a significant and expanding clinical, and basic science, research literature relating to the behavioural and mental health needs of people with PWS. Many clinical studies have identified and characterised the extent and nature of the neuropsychiatric phenotype of PWS.

Clinical studies, including neuroimaging, and basic science research using genetically modified mouse models of PWS, have begun to elucidate possible underlying mechanisms that may explain the occurrence of the neuropsychiatric phenotype. Understanding is undoubtedly advancing.

Studies and clinical trials have been conducted or are currently in progress to examine the impact of early intervention on later development, as well as the effectiveness of psychological treatments and vagus nerve stimulation in preventing emotional outbursts.

Pharmaceutical companies are carrying out clinical trials of medications, particularly for the treatment of hyperphagia, but also for emotional outbursts, sleep disorders, and for optimising social functioning.

1.1.4 The support and care of children, and of many adults, with PWS is undertaken by their families. It is the family who has had to overcome the early challenges of caring for an infant with PWS and then later manage the over-eating behaviour (hyperphagia) that develops, along with other behavioural and mental health problems associated with PWS.

If available, health support is usually led in childhood by paediatric endocrinologists. However, effective health support also requires the expertise of other disciplines including dietetics; physiotherapy; speech therapy; clinical psychology; and those working in child development, and in child and adult mental health or intellectual disability services.

The transition to adult life presents new challenges, and it is often during this period that individuals with PWS may experience a decline in behaviour and/or mental health. Additionally, there is a heightened risk of obesity, as increased independence can lead to unrestricted access to food. During this time, informed and high-quality social support is likely to be essential.

1.1.5 One person with PWS is quoted as saying:

> *"I am a person like you are but sometimes the PWS is on my shoulder and then I need help."*

In the workshop held during the IPWSO conference in Limerick in 2022 for adults with PWS, many described their struggles with mental ill health and with their eating behaviour.

For another person, it was his grief following a significant family loss that nearly overwhelmed him. For those people with PWS in the workshop from across the world it was access to informed support and understanding that was so crucial.

1.1.6 The above quote and the discussions in the workshop illustrated the importance of both recognising the person with PWS and their individual qualities, strengths, and circumstances, and also acknowledging the disabilities that arise as a consequence of having PWS.

People with PWS have their own strengths that can be built on. Early knowledge about the syndrome can help parents understand the needs of their child.

Growth hormone supplementation, although it does not affect the hyperphagia, promotes better growth and increases muscle strength in childhood.

Early intervention and informed support at home and school can optimise behavioural, cognitive, and social development. Finally, children with PWS can be helped in childhood to better prepare for their future as adults.

1.1.7 However, the various challenges facing people with PWS and their families should not be underestimated, as there are likely to be many.

There is still much to discover about how best to promote and maintain the quality of life of people with PWS over time. There is also more to be understood about the possible reasons for the specific difficult behaviours of concern and mental health problems known to be associated with PWS. Why do they occur? How can they best be prevented? What interventions work?

Families report that these behavioural and mental health issues are particularly disruptive to family life and challenging for them to manage. They have a significant impact on the lives of children and adults with PWS and that of their parents, siblings and wider families.

However, our message is a positive one - we believe that with professional knowledge, understanding, empathy, and informed support, much can be done to improve the mental health and quality of life of people with PWS, even when financial and personal resources and services may be limited.

1.2.0 The policy context: practices, rights, laws, and conventions

1.2.1 As an international group we recognise that, in addition to individual, cultural and family differences, the support and treatment of children and adults with PWS and also of others with different neurodevelopmental syndromes, takes place within the national policy framework and service structures of the country where the person with PWS lives. Whilst acknowledging vast differences between countries in financial and human resources, and differences in access to medical and social services, it was agreed that as a group we must aspire to the core principles set out in UN International Conventions.

1.2.2 Following a history of neglect and abuse of people with intellectual disabilities there has been a strong and positive move towards ensuring the rights of people with disabilities are protected, and that services are available to promote full inclusion in society.

International and National Declarations and Conventions relating to human rights and fundamental freedoms apply to all populations, including children and adults with disabilities. It is, however, the UN Convention on the Rights of Persons with Disabilities (UN CRPD) that specifically sets legally binding principles, which inform the support of people with disabilities in those countries that have ratified the Convention. IPWSO supports these principles.

1.2.3 As this Report outlines, people with PWS have complex health and support needs that require access to appropriate health care and high-quality support.

In high-resource countries, healthcare access may be provided at no cost at the point of contact; based on means testing; or covered by health insurance. Support and treatment for those with PWS and their families may come from government sources and/or the private sector.

In contrast, some countries have very limited services for rare disorders and lack the necessary health expertise and genetic diagnostic resources.

Organisations in the third sector, such as rare disease charities and National PWS Associations, play a vital role in providing information and support for rare diseases. These differences, both within and between countries, significantly affect the availability and type of services available to people with PWS and their families.

1.2.4 IPWSO supports the World Health Organization's Universal Health Coverage (UHC) campaign advocating affordable healthcare available to all, including those born with a rare disorder such as PWS.

This goes beyond just meeting physical health needs, and must include access to services that can meet complex behavioural and mental health needs, ensuring that expert support is available to families and others when it is required.

International, Regional, and/or National Laws and Conventions described in 1.2.2 highlight the human rights of people with disabilities, and prohibit discrimination on the grounds of disability. They acknowledge the need for, and importance of, providing additional support for children with disabilities in schools, as well as offering assistance to families and services that promote independence in adulthood.

1.2.5 People with PWS have very specific needs relating to their mental health and their behaviour. Some of the syndrome-related behaviours can lead to ethically and legally complex situations, especially as individuals gain more independence in adulthood.

For example, an adult with PWS may wish to make their own decisions about food or finances, 'choosing' to have unrestricted access to food. As a consequence, life-threatening obesity is likely. When certain behaviours pose a risk of harm, health or social services may intervene. This can create situations where different rights are in conflict, such as the right to privacy and autonomy in making decisions as an adult, versus the right to life, particularly when unrestricted food access leads to life-threatening levels of obesity.

How these potentially conflicting rights are balanced raises important questions, including what parents and individuals with PWS should expect from health and social care services in these situations (See Murray et al., 2021 for discussion of legal cases involving people with PWS).

For people with PWS and their families, access to informed healthcare and social support, regardless of the ability to pay or where they live in the world, is essential. Such support needs to recognise the complexity and specificity of need associated with having PWS, and importantly, include access to expertise with respect to behaviour and mental health, as well as physical health.

The support of children and adults with PWS requires acknowledging the tensions between individual rights. It is important to help people with PWS understand the nature of the syndrome, while ensuring that informed support is available and accepted with the agreement of everyone involved.

1.3.0 Aims of the Report

1.3.1 For families and clinicians who are new to PWS, one problem that exists is the lack of guidance and no agreed best practice documentation for the assessment, prevention and treatment of the various clinical conditions that make up the neuropsychiatric phenotype that is characteristic of PWS. This is further complicated by there being significant differences between the disciplines involved, and across different regions of the world, in the terminology used to describe the behavioural and mental health issues associated with PWS and how they are best understood and managed.

Although there are rarely simple and single solutions, with advancing knowledge and an expanding research base, where expertise is available, informed interventions can make a difference to the life of a person with PWS and that of their family.

This Report draws on research evidence, expert clinical opinion, and the experiences of affected families, professional care providers, and people with PWS to identify those components that it is agreed contribute significantly to a good quality of life and stable mental health in children and adults with PWS.

The IPWSO Mental Health Network

IPWSO has brought together parents, clinicians, behavioural experts, and professional care providers with the aims of bringing clarity to a complex field, defining the issues, setting out the present state of knowledge, and providing best practice guidance on support and treatment.

1.4.0 How this Report was prepared

1.4.1 This Report was prepared by the global membership of the IPWSO Mental Health Network, and was discussed in draft form at a special mental health workshop held in Limerick, Ireland in July 2022.

Through the Network, people with PWS were informed of this initiative and were asked to contribute descriptions of their experiences – these are illustrated in the quotes included in the Report.

Also, at the IPWSO International Conference held in Ireland, in 2022 a group of adults with PWS were asked to share their experiences relating to their mental health. This meeting was held with the support of Gary Brennan of the Prader-Willi Syndrome Association of Ireland (PWSAI), and attended by Tony Holland on behalf of the Mental Health Network. With their permission, comments from this workshop are included in this Report.

The final version of the Report has been agreed by the membership of the Network and by the IPWSO Trustees.

1.4.2 For the development of the shared best-practice guidance included in Part 5 of the Report, the process that was followed was an iterative one, with virtual workshops devoted to each of the broad topic areas set out below. Given the differences in time zones, discussions of the same topic were arranged for morning and evening sessions (UK time) so as to ensure that all members of the Mental Health Network would have an opportunity to attend.

For many of the topic areas, recent literature reviews already existed. In addition, a member of the group (Joyce Whittington) has since 2018 been responsible for compiling quarterly lists of all scientific papers published on PWS on behalf of IPWSO. These are published on IPWSO's website. Where necessary, additional focused literature reviews were undertaken.

Summaries of the discussions were prepared after each meeting, and made available to the network, and were the basis for subsequent discussion and refinement.

Context of Prader-Willi syndrome

1.5.0 Overview of PWS

1.5.1 In this section, for those who may be unfamiliar with PWS, we summarise the diagnostic features present at birth and later in life, give an overview of the genetics of PWS, and provide other information that informs the rest of the Report.

For a more comprehensive description of the genetics and main diagnostic characteristics of PWS, references are listed in the Appendix. Information on all aspects of PWS is also available on the IPWSO website, also on many National Association websites.

1.5.2 Our understanding of PWS has advanced considerably since the clinical characteristics of people with the syndrome were first described in the literature by Prader, Labhart and Willi in 1956. **Figure 1** lists some key discoveries and advances in our understanding of PWS, with a specific focus on mental health and behaviours of concern.

Given the importance of an early and accurate diagnosis, IPWSO funds free genetic testing of samples sent by post to the Baschirotto Institute for Rare Disorders (BIRD) for families who cannot afford testing or where it is not available

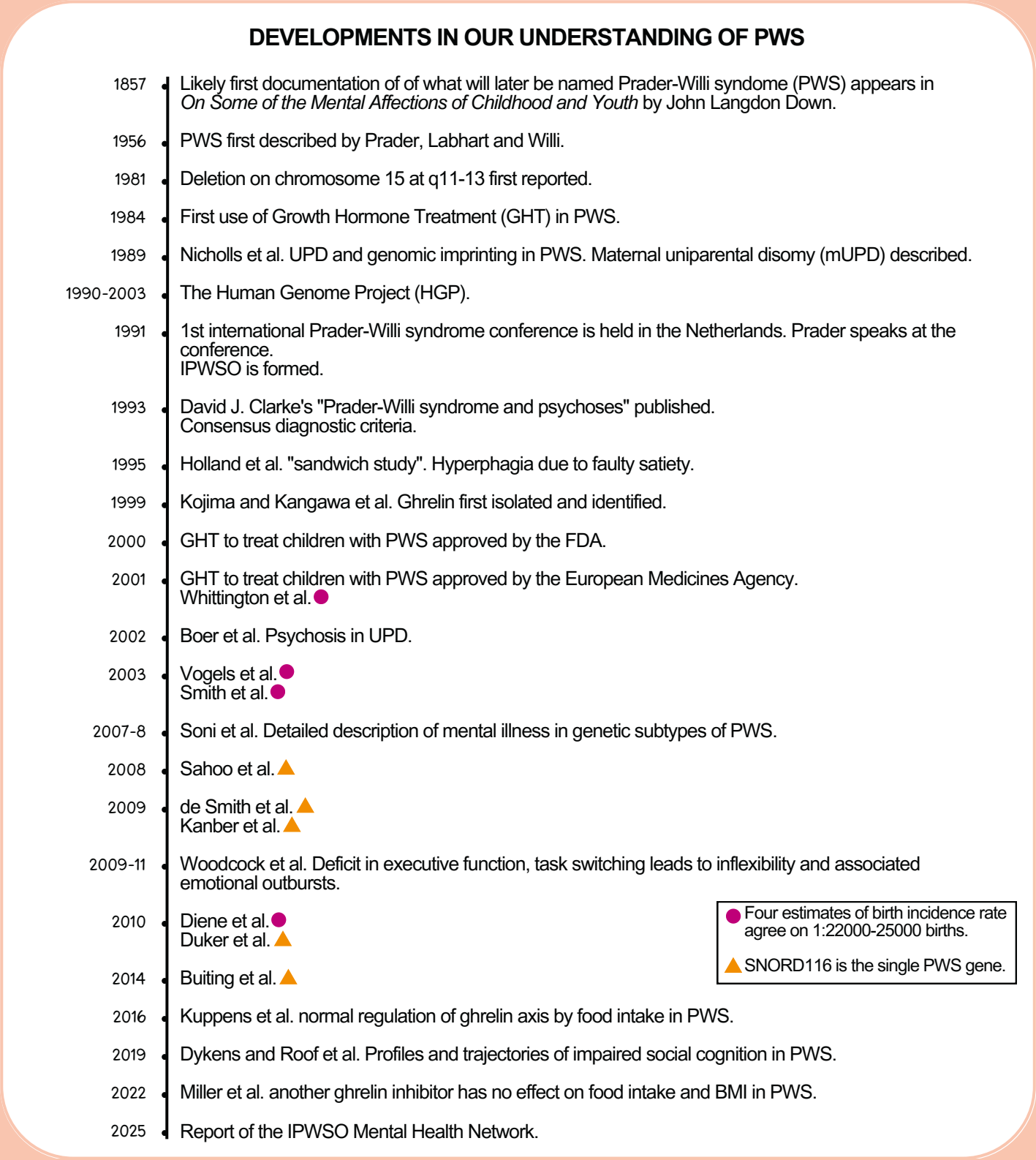


Figure 1 Timeline of selected discoveries in PWS

1.5.3 As illustrated in **Figure 1**, since the 1990s, PWS has been recognised as a complex neurodevelopmental condition which is genetically determined. It results from the absence of expression of one or more specific genes located in the part of chromosome 15 referred to as 15q11-13 (Driscoll et al., 2024). These genes are distinct from most others in the human genome because only the paternal copies (alleles) are expressed, while the maternal copies are 'imprinted' and not expressed. PWS occurs when at conception the normally active paternal copies of these genes are absent, or are present but are not expressed.

This can happen for one of the following reasons:

- **Deletion:** a small deletion on the paternally-inherited chromosome 15 (different sized deletions have been reported) in the 15q11-13 locus (delPWS).

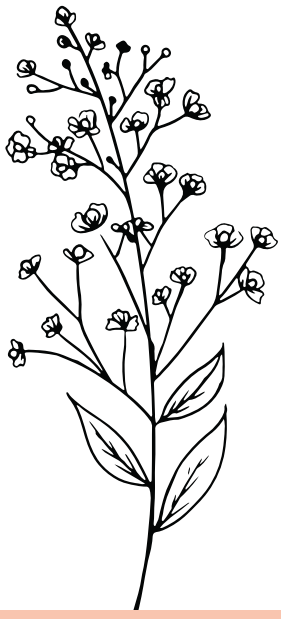
- **Uniparental maternal disomy (mUPD):** both chromosome 15s are of maternal origin, and the paternal copy is lost (mUPD).

- **Imprinting Centre Defect (ICD):** the presence of 'an imprinting centre' defect, which, from a genetic perspective, is similar to having a mUPD (ICD).

1.5.4 The two most common causes of PWS (deletion and mUPD) are present from conception. They are described as 'de novo' as they have occurred by chance in that baby. Neither chromosome 15 deletions nor mUPDs are present in the chromosomes of a parent. The rare imprinting centre defect (ICD) genetic abnormality may be inherited.

The fact that a baby is born with PWS is no one's fault. However, in addition to feelings of anxiety about their child, parents may feel they or their partner are in some way responsible. People with PWS may also harbour feelings of blame towards their parents. These unfounded beliefs, though irrational, can become significant psychological concerns. If they persist, addressing them through psychological support and/or genetic counseling is essential.

After a diagnosis of PWS, giving support to parents so they can understand the reasons for their baby's difficulties helps families provide the best care. National PWS Associations and IPWSO are key resources at this time.



1.5.5 Although the two main genetic types of PWS share core features, genetic differences between these subtypes (deletion and UPD) as well as between those people with PWS with different sized chromosomal deletions may explain some of the phenotypic differences that are observed between individuals with PWS. The paternally-expressed gene cluster, SNORD116, encoding small nucleolar RNAs is considered the key candidate gene. The lack of its expression is thought to be a primary cause of PWS. (Duker et al., 2010, Sahoo et al., 2008).

(See **Figure 2** for schematic representation of the genetics of PWS and the imprinted and non-imprinted genes at 15q11-13.)

In PWS there will also be the absence of expression of other genes located at 15q11-13, which are also maternally imprinted. These include MKRN3, MAGEL 2, Necdin (NDN), PWSRN1 and 2, SNURF-SNRPN complex, and SNORD 115.

In those with the mUPD form of PWS, the expression level of the paternally imprinted gene, UBE3A, will be increased by 50% compared to those with the deletion form. The extent to which gene expression differences influence the phenotype remains debated.

In those with the deletion form of PWS, the expression levels of non-imprinted genes (NIPA1, NIPAY2, CYFIP1 and GCP5) that are located between chromosomal breakpoints 1 and 2 will be reduced in those with Type 1 deletions (deletion between chromosomal breakpoints 1 and 3) only. Three genes coding for GABA receptor subunits are located proximal to breakpoint three. These genes are biallelically expressed in the brain (i.e. not imprinted). However highly skewed allelic expression has been observed in the brains of people with autism and others with Retts syndrome, suggesting that epigenetic dysregulation of these genes is common in those disorders (Hogart et al., 2007).

Given the role of GABA as the main inhibitor neurotransmitter in the brain, this may be of relevance to the causation of mental ill health in people with PWS.

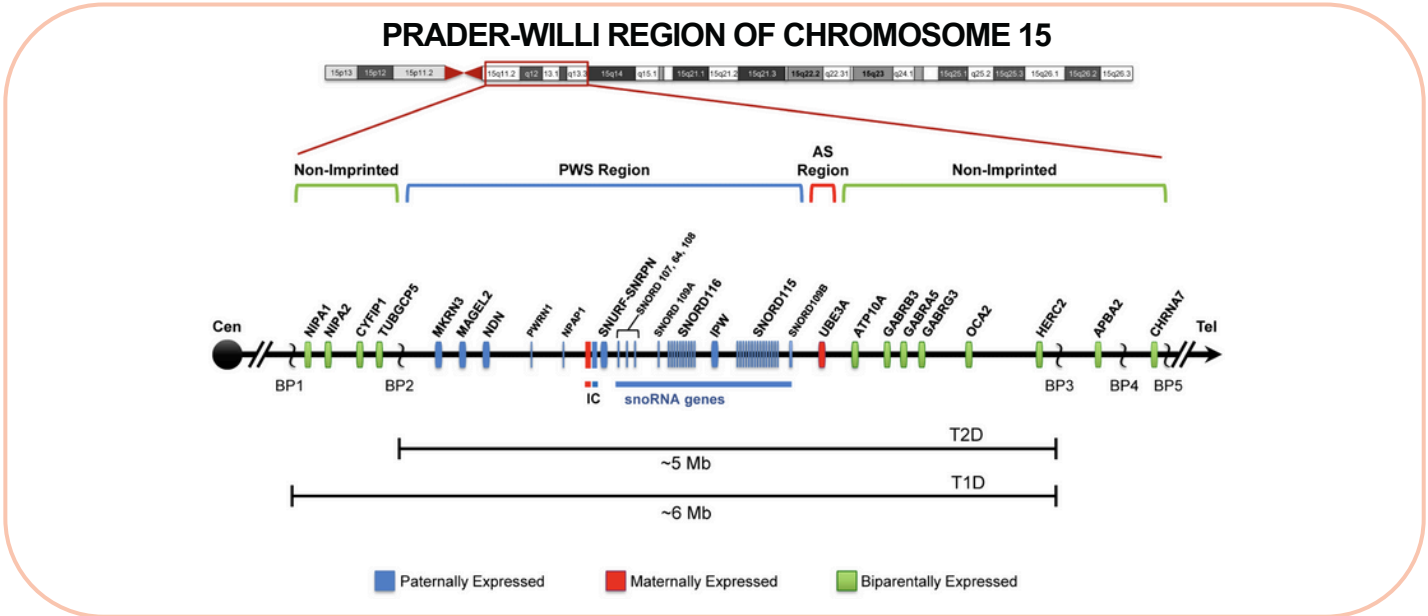


Figure 2 Summary of the genetic and expression map of chromosome region 15q11.2-q13.3. Adapted from Driscoll et al., PWS GeneReview (2024, p. 7)

1.5.6 The process by which specific gene copies (alleles) are imprinted is known as 'epigenetics'. This is key to understanding the genetic causation of PWS (see also detailed review on epigenetics by Eggerman et al., 2021). The role of epigenetic modifications in understanding the phenotype of people with PWS will be considered further in Part 4.

In summary:

a) Maternal imprinting at locus 15q11-13: Specific genes in the15q11-13 region (see Figure 3) are imprinted as a result of epigenetic processes. If the paternal copies are absent for the aforementioned reasons, the characteristic early PWS phenotype, common across all genetic types, becomes evident.

b) Link between early and later PWS phenotypes: The connection between the early PWS phenotype and the later PWS phenotype, especially hyperphagia, remains uncertain. However, a possible mechanism includes the epigenetic modification of genes important in the hypothalamic feeding pathways, leading to dysfunction of satiety mechanisms.

c) Gender-specific epigenetic effects and genotype variation: Gender-dependent epigenetic modification of other imprinted genes at 15q11-13, depending on whether they are inherited from the male or female line, could contribute to the risk for the broader PWS phenotype, such as the risk of skin picking, or explain phenotypic differences that depend on variations at the level of the genotype (deletion size, deletion vs mUPD vs ICD).

d) **Environmental influences on epigenetic changes:** Epigenetic modifications may explain how positive and negative environmental factors in childhood affect later development. For example, early hypotonia and the associated reduced sensorimotor input and limitations in social interaction in infancy may lead to epigenetic changes in neural pathways that are crucial for normal motor and social development.

1.6.0 PWS phenotypes and their implications for physical health

1.6.1 In 1993, Holm et al. set out the major, minor, and supportive criteria, which are still considered to be characteristic of the PWS phenotypes. The primary phenotypes have been described as:

a) Neonatal phenotype:
The first phenotype, present in utero but mainly noted at birth is characterised by:

- extreme hypotonia (floppiness)
- the infants are usually low or low/normal weight for gestational age
- evidence of failure to thrive
- immature development of the external genitalia (undescended testes in boys and small labia in girls)
- Augmented feeding is usually required because of a poor suck.

b) Early childhood phenotype:
Emerging in early childhood, this phenotype includes:

- signs of general developmental delay, and delay in the acquisition of functional, and later cognitive and educational abilities
- evidence of reduced growth (unless growth hormone supplementation is given)
- impaired sexual development due to hypothalamic sex hormone deficiency
- a switch from an apparent reluctance or inability to feed to the onset of excessive eating (hyperphagia – this is described in greater detail later in the Report)
- a significantly increased risk for other behaviours of concern and mental ill health.

During this time, extreme obesity can develop if access to food is not well regulated. Without restrictions in place, the energy intake of the child is greater than their overall energy requirements, including meeting their growth needs (see IPWSO guidance).

Awareness of this risk of severe, potentially life-threatening obesity and the need for early intervention is very important in this transition phase from hypo- to hyperphagia.

c) Adolescent and adult phenotype:
In adolescence and adulthood, individuals with PWS face continued risks, including:

- severe, potentially life-threatening obesity, often due to increased independence and unsupervised access to food
- escalation of behavioural challenges and mental health issues, such as mood disorders
- physical health risks, particularly if the individual is very overweight and also if other possible medical problems are not treated, for example, diabetes mellitus, hypogonadism, hypothyroidism and osteoporosis.

Understanding PWS, implementing obesity prevention strategies, and recognising factors contributing to the presence of behaviour and mood problems are crucial to ensure a positive life-trajectory. These issues are addressed throughout the Report.

1.6.2 The diagnostic criteria focus on the presence of specific physical characteristics, limitations, and disabilities that research and clinical experience has identified as indicative of PWS. However, people with PWS also have strengths, and an increasing part of assessment is to identify those strengths so that the person with PWS can be supported to build on these.

Whilst at birth the phenotype is likely to vary, where early diagnosis and intervention is available, the picture of the phenotype in childhood and later life may be very different. For example, severe obesity is less apparent if a child grows up in a food-managed environment, and if they and their family have a better understanding of the need to manage access to food.

Similarly, those who start taking growth hormone early in life will be closer to their target height, will not have all the physical features associated with the syndrome, such as the facial characteristics, and will have a normalised body shape provided they are not obese. In addition, early and informed support from parents can positively influence the development of people with PWS and their developmental milestones.

More recent evidence has also shown some benefits targeting social cognitive abilities through early intervention with children with PWS aged 6 to 9 years (Dimitropoulos et al., 2024). For these different reasons, the phenotype of people with PWS will vary within and between countries.

1.6.3 The transition between early childhood and the later phenotype illustrates the fact that the PWS genotype, which is present from conception, has not only a significant impact on the development of the baby in-utero, but also throughout the developmental phases of childhood and into adult life. The caring environment also influences outcomes early in life, and can have an impact on future developmental milestones.

For example, the fact that a baby with PWS is hypotonic means that it cannot easily move its limbs, as do typically developing babies, which can further delay motor development.

Similarly, a baby with PWS may have difficulties forming a close attachment to their mother and father and other significant adults through no fault of the parents. We anticipate that this may further impact on subsequent social development, even though the parents and others involved have good bonding qualities.

1.6.4 Sethuntsa (2018) has proposed a link between the physiological challenges that children with PWS experienced from infancy, and subsequent behaviour problems, particularly those related to the inability to maintain emotional control.

She argues this could be further explained by child developmental theories, as described by Calkins, Perry & Dollar (2016). They reported that the first two years of an infant's life are characterised by growth in physical, psychological, and social skills, particularly the infant's ability to self-regulate, defined as the ability to control emotions and behaviours, in order to cope effectively with environmental demands across a variety of contexts.

The ability to regulate at these levels emerges, at least in a rudimentary form, during the perinatal period (e.g. sucking, head turning, reaching and touching, gaze aversion, self-soothing), and continues throughout early childhood. These activities and social interactions help infants learn the connection between their arousal, behaviour, and environmental responses, something which is fundamental to their developing awareness of their own ability to control their behaviour and attention (Calkins et al., 2016).

This may be very difficult for individuals with PWS to achieve, for example, due to hypotonia.

1.7.0 Physical illnesses associated with PWS

1.7.1 PWS is associated with a high risk of specific physical illnesses that, for the reasons set out below, may go undetected and therefore untreated (Pellikaan et al., 2020).

Such physical morbidity is also associated with increased mortality rates across the lifespan (see systematic review by Bellis et al 2021). This increase in morbidity and mortality is largely due to hyperphagia and the development of severe obesity or choking and/or events of aspiration and resulting respiratory complications.

Type 2 diabetes mellitus and obstructive sleep apnoea (central sleep apnoea can also occur) are common and related to levels of obesity. Also, untreated hormonal deficiency can lead to early ageing, muscle weakness, and osteoporosis.

Maintaining good physical health and being aware of how potentially life-threatening illness may present is a central part of good care.

Whilst having PWS is associated with such risks, the severity of problems like obesity largely depends on the level of support provided and how well the food environment is managed.

Key considerations include:

- **Hyperphagia and resultant obesity:** associated with increased rates of physical illness and mortality.

- **Dysphagia and respiratory risks:** Dysphagia, caused by excessive or rapid eating, and oesophageal hypotonia are associated with choking and aspiration and can result in serious respiratory complications.

- **Obesity related conditions:** such as sleep apnoea, which in turn can affect mental health. Obesity-related limitations on mobility may affect physical health and quality of life.

- **Behavioural impacts of physical illness:** Physical health issues can manifest in an increase in the frequency and/or severity of problem behaviours, or the emergence of other undesired behaviours. For example, severe constipation may affect mood or aggravate rectal picking, both of which can be life-threatening.

- **Monitoring behaviour changes:** Families and clinicians need to ensure that when the severity of existing behaviours changes, or new behaviours of concern emerge, underlying causes are identified and addressed with appropriate interventions. As highlighted in Parts 4 and 5, changes in behaviour may be due to changes in environmental conditions or the increase in or recurrence of a physical or mental illness.

1.7.2 Physical illness may go unnoticed unless it is specifically enquired about.

Several factors can lead to delayed or atypical presentations of physical illnesses, meaning that these conditions might not be suspected or diagnosed until they have significantly progressed. Such undetected illness may not only impact the quality of life of the person with PWS, but also on that of their family, which in turn may further negatively affect the individual with PWS.

Health professionals and those providing support must be aware that people with PWS may struggle to communicate the nature and severity of their symptoms, and the factors listed below may make the identification and diagnosis of physical illness more difficult.

- A high pain threshold
- Absent, or reduced, vomiting reflex
- Abnormal temperature regulation

1.7.3 Eating excessive amounts of food can be associated with paralysis of the stomach so that it cannot empty (gastric paresis) and can also lead to a ruptured stomach (gastric rupture) (Stephenson et al., 2007). Severe constipation may occur as a result of gut muscle hypotonia, over-eating, and a failure to recognise the need to defecate.

All of these are acute and life-threatening conditions, requiring immediate medical attention. While it may not always be possible to prevent such problems, the level of risk can be reduced by the knowledge of those providing support and the implementation of preventative strategies.

If there is a significant change in the mental state and/or behaviour of someone with PWS, it is important to consider whether there is a physical explanation or whether this is a result of deteriorating mental health.

If this change is associated with complaints of pain, the presence of vomiting, or general signs of illness, a physical cause is likely, and urgent medical advice should be sought (see IPWSO medical alerts).

Information on physical health and medical alerts can be found on the IPWSO website.
www.ipwso.org/pws-information/

1.7.4 Key moments in the life of a person with PWS, as described in **Figure 3**, often coincide with developmental and environmental vulnerabilities, where the risk of negative outcomes is highest.

These transition periods include events like starting school, where the child must adjust to new academic demands, navigate a complex social environment, and separate from the safety of home and parents. Cognitive and social deficits that were previously unnoticed might now become apparent. This may in turn impact learning and behaviour.

Some families describe that while their child may manage well in primary school, the move to secondary school may be a major trigger point for a deterioration in behaviour. This is often due to the widening cognitive gap between typically developing peers and a child with PWS.

The early teenage years are also a time when, both in the typically developing population and in people with PWS, the risk of mood disorders and major mental illness increases and such illnesses may become apparent for the first time, further impacting on general functioning and behaviour.

For teenagers and young adults with PWS, feelings of anxiousness may increase, due to increased access to food, particularly in schools or colleges. During these transitions, access to informed support is often crucial for families.

To understand the mental health needs of children and adults with PWS, it is important to consider the developmental impact, and the interactions between the person and their life circumstances.

For families, access to support from child development, health, social or education professionals can be pivotal during these key life transitions.

IMPORTANT POINTS IN THE LIFE OF A PERSON WITH PWS

Pregnancy

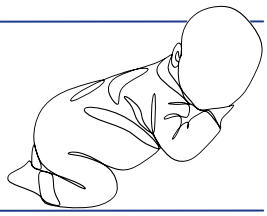
Apparently normal development of internal organs but not brain.
Polyhydramnios can be seen.
Foetal movements may be reduced or absent – hypotonia already established.
Decreased foetal growth.

Birth

Assisted delivery may be needed.
Birth weight can be lower than normal.

Newborn and infancy

Severe hypotonia and failure to thrive. Augmented feeding.
Genetic test and diagnosis of PWS.
Late milestones.
Sleep investigations for potential sleep apneoa.
Start of Growth Hormone Treatment (GHT) possible in infancy.



Pre school years

GHT can also be started during this period.
Development of hyperphagia.
Development of aberrant behaviours:

- Repetitive questions or speech
- Skin picking
- Temper outbursts may arise and it is sometimes difficult for the child to calm down.

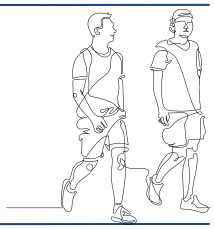
Maintain routines.
Early interventions and encouragement of socialisation.
Keep food in optimal quantity and quality.

Early school years

Initial cognitive assessment to mark areas of strength and weakness and learning difficulties.
Introduction to the school environment.
Assess for sleep-disordered breathing as a potential adverse factor for behaviour and learning outcomes.
Finding the right educational setting to adapt to specific learning and cognitive requirements.
Aberrant behaviours can increase.
Short stature if not on GHT.
Risk of bullying and/or not making peer relationships.

Adolescence

Increased out of home socialisation can be seen.
Awareness of difference from peers' and siblings' lifestyle can increase.
Wanting the same as others.
Supported socialisation.
Increased propensity for psychotic change may be possible.
Increased caregiver fatigue and burden can be seen.



Early adulthood

Finishing school.
Change from child to adult services.
Transition to new accommodation.
Hyperphagia may be more difficult to control.
Often few peer relationships, but can enjoy activities with others
Some will experience the start of mental health problems, but not all.

Adulthood

Supporting capabilities.
Daytime occupations/purposeful days.
Seeking the right occupation.
Seeking appropriate supports.
Loss of self-esteem and mental health problems will arise for some, but not all.
Often few peer relationships, but may enjoy company.

Ageing

Appropriate, supported environment.
Regular general health checks.
Supported socialisation.

Figure 3 Examples of transitions in the life of people with PWS and factors that might predispose to mental ill health at such times.

1.7.5 In adolescence, supplemental sex hormone treatment is required to enable secondary sexual development. Such treatment is not available worldwide, and even if available, it may not be offered, or its use may be viewed with concern (Eiholzer et al., 2021).

The onset of sexual feelings and relationships has not been investigated in a systematic way. However, it is clear that teenagers and adults with PWS do form both heterosexual and homosexual attachments. These can be intense, but sometimes only last for a short time.

Men and women with PWS report being fond of and wanting children. Men are not thought to be fertile, but a small number of women with PWS have become pregnant (see Poitou et al., 2022 for an overview of transition into adult life, and Shaikh et al., 2024 for consensus guidance for children and during transition).

1.7.6 As discussed later in the Report, although transitions in the lives of people with PWS can be challenging, careful planning, the presence of informed teachers and caregivers, and educational organisations that are willing to make reasonable adjustments to accommodate the special needs of a child with PWS can mitigate the impact of these moments.

Early diagnosis, access to information, support and medical expertise, and an understanding of how PWS specifically affects the child are all important factors that can make a difference.

Content of the Report

1.8.0 How we approach different types of evidence

1.8.1 There are considerable gaps in our knowledge about PWS, and only recently have 'gold standard' clinical trials for interventions targeting specific aspects of the syndrome been developed. However, the membership of the group has considerable experience in the assessment and treatment of the various behaviours of concern and dimensions of mental ill health in this population.

Where appropriate, in accordance with good practice, we have set out the level of evidence, including whether our statements are based on:

- Peer-reviewed publications
- Systematic or structured reviews
- Expert opinion
- Case reports and case series

1.8.2 For Part 4, which focuses on assessment and treatment, the nature of the evidence is set out, including findings from:

- Clinical trials
- Proof of concept studies
- Expert opinion
- Case reports and case series

1.9.0 Outline of the remaining sections of this Report

1.9.1 The membership of the Mental Health Network was tasked with developing consensus practice guidance for:

- The assessment, prevention and treatment of mental ill health, including behaviours of concern that commonly impact the lives of people with PWS and the lives of their families and others who support them.
- Enhancing and maintaining the quality of life and associated personal well-being and mental health of people with PWS.

1.9.2 The main topic areas covered by the Report and in the Appendices are set out below and **Figure 4** illustrates the core content and the different parts of the Report that cover each topic.

a) An introduction to the Report and to PWS: including the genetics and phenotypic characteristics and the associated physical illnesses that may impact on life-expectancy and on mental health and quality of life of people with PWS **(Part 1).**

b) Terminology and definitions: including well-being, quality of life, mental health, mental ill health, and mental disorders in people with PWS, the inter-relationship with environmental circumstances, and the factors that are known to influence the above **(Part 2).**

c) Dimensions of mental ill health associated with PWS: including the impact of atypical brain development on cognitive functioning, and descriptions of those behaviours of concern and the dimensions of mental ill health associated with PWS **(Part 3).**

d) Identifying determinants and understanding causal mechanisms: our agreed understanding of the mechanisms that lead to the development and potential persistence of mental health conditions, and the inter-relationship between an individual´s vulnerability and past/present social and environmental circumstances **(Part 4).**

e) Shared practices in the assessment of mental ill health: including behaviours of concern, and their prevention and treatment for people with PWS, and the promotion of quality of life **(Part 5).**

f) Significant open questions and future research: at the end of the Report, we identify remaining areas of concern and areas where research is needed to provide a better understanding of why people with PWS have such a high risk for mental ill health, along with potential new treatment options **(Part 6).**

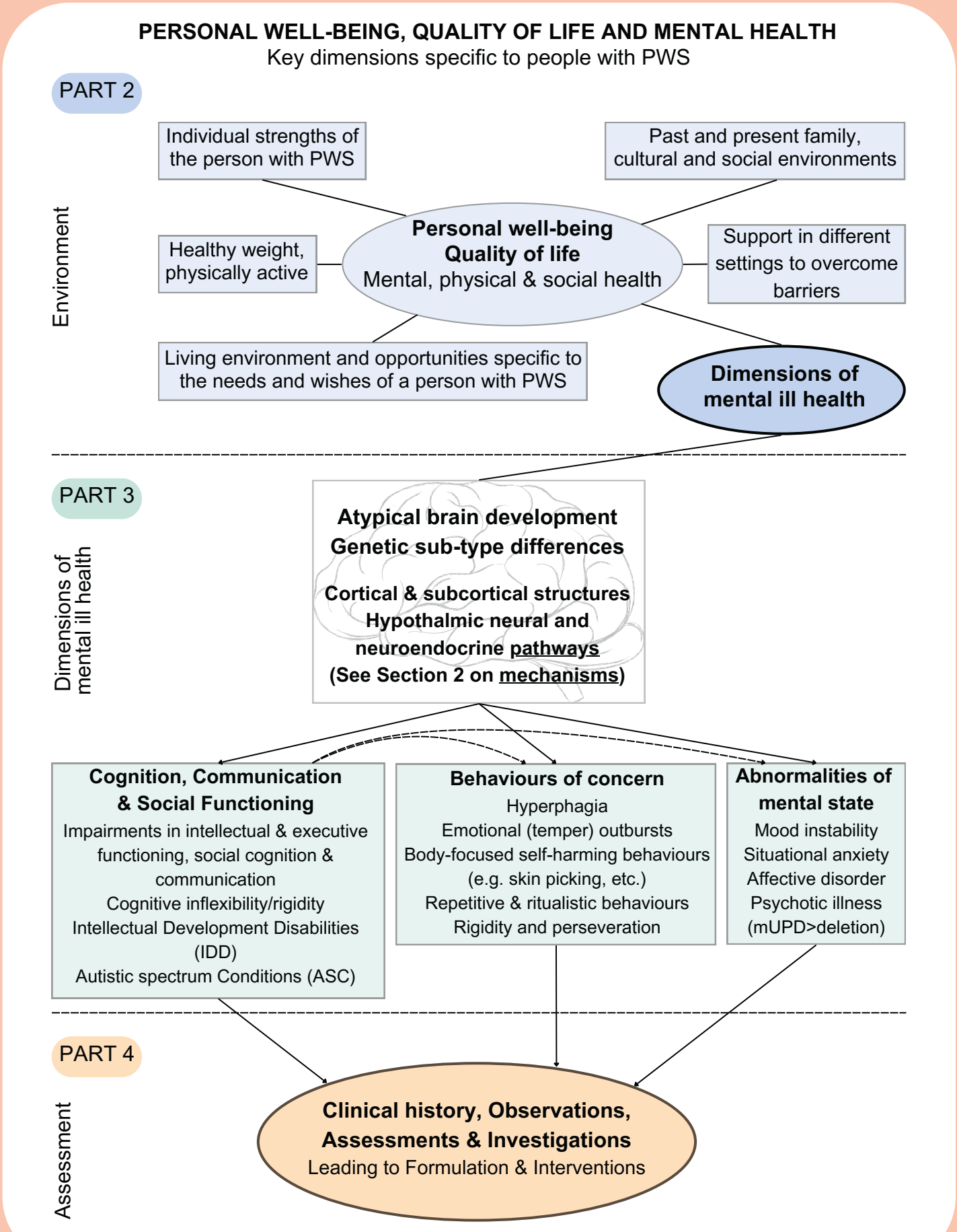


Figure 4 illustrates the different components that need to be considered and evaluated, including: individual strengths and the support environment; neuropsychological/cognitive dimensions, which can be formally measured; behaviours of concern that are usually observed by others, which above a certain level of severity/frequency impact on mental health and quality of life and disturbances of mental state. The latter may vary in severity, and when above a particular threshold, may meet established diagnostic criteria for mental illness.

By providing knowledge and understanding of PWS and information about the factors that a) contribute to good quality of life and good mental health, and b) increase or decrease the risk for mental ill health, we can assist parents, health professionals and care providers to support an individual with PWS within the context of that person's unique abilities, life experiences, and circumstances.

1.9.3 This Report provides a comprehensive description of the outcomes and the conclusions drawn from the IMHN discussions, setting out the opinions of the group as a whole.

Based on the work summarised in this Report, additional shorter papers will be prepared for families, care-providers, and health professionals. These will be made available in different languages and, where appropriate, submitted for publication in clinical and scientific journals.

1.9.4 In conclusion, Part 1 has set out the context for the Report, and has given a brief overview of the PWS genotype and phenotype and outlined some of the key concerns with respect to physical illness. Behaviours of concern and mental ill health, as they affect people with PWS, cannot be seen in isolation.

In subsequent parts we argue that mental health is more than the absence of mental disorder and includes concepts such as quality of life and personal well-being.

Addressing these issues requires a comprehensive and holistic approach that considers the welfare of the family and the extent to which there is access to adequate support and opportunities that enable people with PWS to thrive.

Part 2: Terminology and definitions

Introduction

2.0.0 The importance of definitions

2.0.1 Differences in terminology and theoretical perspectives were noted among network members, likely reflecting the group's diverse composition, which included individuals from various countries, health disciplines, and roles, such as parents and support staff.

For example, within psychology and the behavioural sciences, the principles of applied behavioural analysis are embraced in some countries but viewed negatively in others. Similarly, some members of the network emphasised a diagnostic biomedical approach, while others favoured behavioural or systemic perspectives.

2.0.2 These differences underscored the need for clear and consistent terminology, especially for a Report intended to be useful globally across settings diverse in their economic status, cultural attitudes, and health and social care structures.

Parts 2 and 3 of the Report, therefore, focus on defining and clarifying key terms. This clarity is essential for integrating research from multiple academic disciplines effectively.

2.0.3 As described below, the definition of mental health has evolved beyond merely the absence of mental disorders. It now encompasses positive attributes, such as the ability to fully engage in society.

In our discussions, parents of children with PWS emphasised that the mental health of their children with PWS extends far beyond a narrow biomedical perspective. For them, good mental health includes broader concepts like 'quality of life' and 'personal well-being', not just for the individual with PWS but also for their family.

While clinical attention often focuses on specific 'dimensions of mental ill health' observed in people with PWS, this broader perspective requires looking beyond what traditional health services deliver.

To truly address quality of life and well-being, it is important to ensure that people with PWS and their families have access to necessary services and support, and that people with disabilities are accepted and fully included in society.

The aims in Part 2 are therefore:

- To describe what is meant by such terms as ‘well-being’, ‘quality of life’, ‘mental health’, and ‘mental ill health’.
- To summarise the different components that are included in their definitions.

Key terms in this Report

2.1.0 Well-being

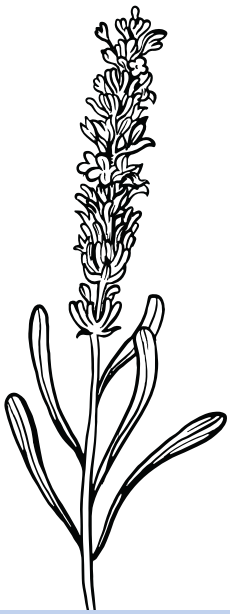
2.1.1 Theories of well-being can broadly be categorised into three main types: “Wanting” theories, “Liking” theories, or “Needing” theories (e.g., Jayawickreme et al., 2012).

- “**Wanting” theories** focus on the fulfillment of rational desires where a person’s desires can be defined objectively. In this approach, well-being is assessed based on a person’s observed choices, such as how much money they are willing to spend to satisfy their preferences. Wanting theories are often used to understand how people seek to enhance their well-being through their life choices and consumption habits.
- **“Liking” theories** focus on a person’s self-reported emotional state, where well-being is assessed subjectively. In this approach, well-being is defined based on a person’s feelings (their emotions or moods) or their personal self-assessments and reflections.
- **“Needing” theories** focus on a person’s welfare as evaluated by external standards, often defined through objective lists of “good things” required for a fulfilling life. These can include factors such as personal autonomy, growth, or a sense of meaning. Notably, this approach recognises that a person can experience well-being without feeling immediate happiness or reporting satisfaction.

2.1.2 The emergence of these three approaches to well-being highlights the often conflicting factors involved in a person’s overall wellness.

For example, while self-reported positive emotions may indicate that a person is enjoying life in the moment, they may not reflect important aspects such as good health, personal autonomy, safety, or genuine fulfillment.

Therefore, well-being is best understood by considering multiple dimensions of well-being, and striving to address all of them comprehensively.



2.1.3 Many psychologists argue that four domains of well-being are important. These domains are sometimes conceptualised as interconnected layers within a "nested model" (e.g., Henriques et al., 2014; see **Figure 5**).

Effective clinical practice aims to enhance a person's well-being across all four domains, as follows:

- **Subjective domain:** The person's self-reported experience of happiness and overall life satisfaction.
- **Health and functioning domain:** The person's biological and psychological health, evaluated against external assessments.
- **Environmental domain:** The quality of a person's material or social environment, including factors such as legal rights, physical safety, and social supports.
- **Values/Ideology domain:** The person's personal reflections on what constitutes a meaningful or 'good' life, encompassing their ethical and moral perspectives.

2.1.4 In PWS, it is essential to address the specific PWS-related issues affecting well-being in each domain, to ensure tailored and appropriate support.

For example:
(a) Subjective domain: People with PWS often express feelings of happiness and joy but are also prone to frequent negative emotional outbursts. Their self-reported well-being must be understood within this dual context, emphasising the need for emotional support tailored to their experiences.

(b) Health and functioning domain: People with PWS are typically driven to engage in behaviours that can compromise their health, such as overeating due to hyperphagia, or experiencing heightened physical sensitivities. As such, their subjective desires need to be balanced against their physical and personal safety. Additionally, they often experience secondary stress from medical challenges like hypotonia, scoliosis, or pain, as well as the anxiety associated with frequent medical appointments and procedures.

(c) Environmental domain: People with PWS are highly sensitive to their surroundings, particularly regarding meal schedules and food availability. Research shows that people with PWS thrive in regulated, structured environments. While they are attentive to social dynamics, their ability to seek or utilise social support may be limited due to impaired social cognition and a tendency toward oppositional behaviour.

(d) Values/Ideology domain: People with PWS are typically well-disposed towards others, articulate, and possess a strong sense of justice. However deficits in executive functioning can hinder detailed self-reflection, contributing to egocentrism and oppositional behaviour.

Considering well-being through these domains underscores the importance of a balanced and comprehensive approach to clinical evaluation, diagnosis, intervention, and support, especially in the specific context of PWS.

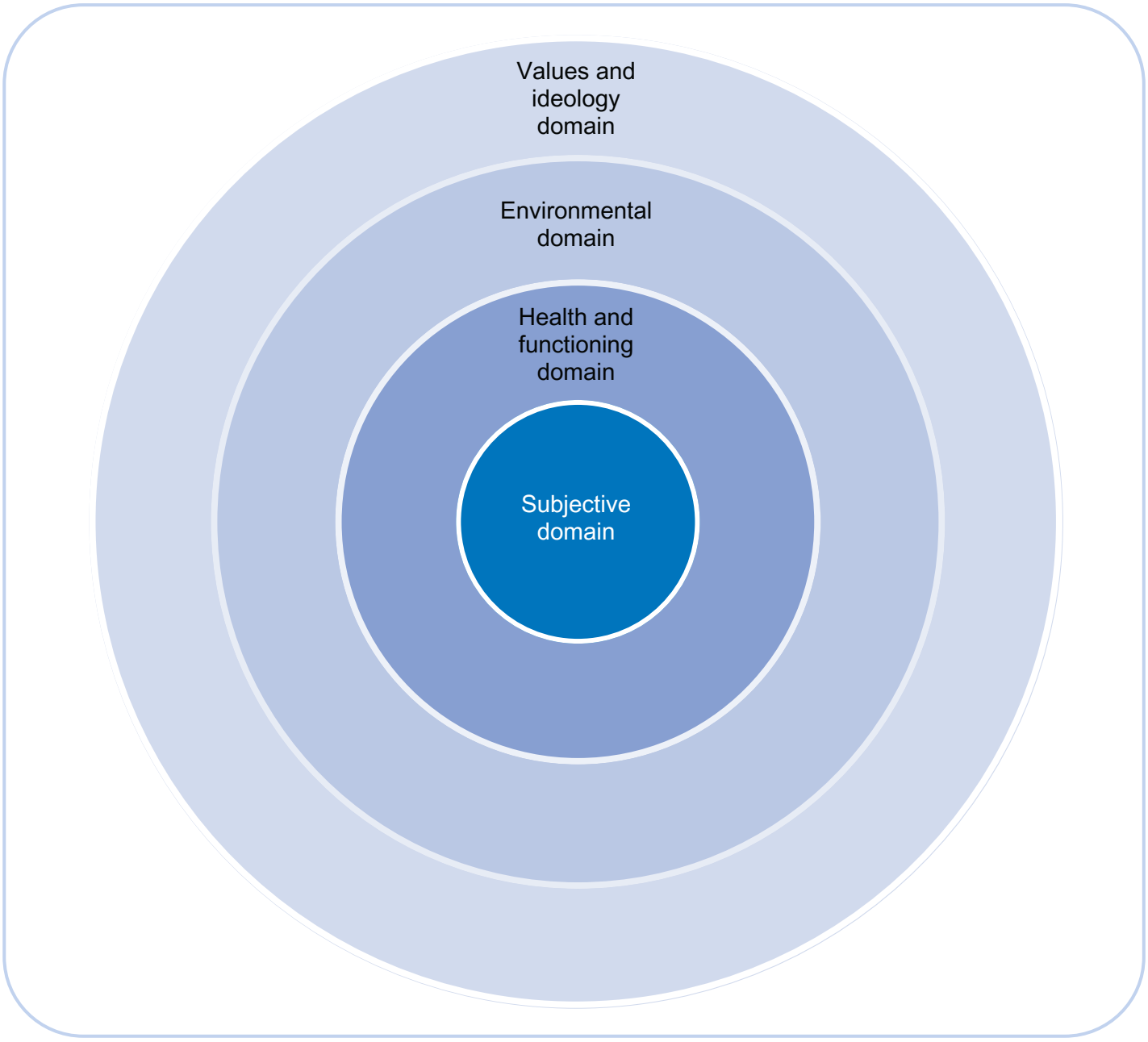


Figure 5 The nested model of well-being (after Henriques et al., 2014).

2.2.0 Quality of life

2.2.1 The term 'quality of life' encompasses a broader scope than 'well-being', covering different areas of a person's life, such as economic status, rights, culture, and health (Fayed et al., 2012). A more specific concept is 'health-related quality of life' (HRQoL), which is widely recognised as a global measure of quality of life (Davis et al., 2006) and aligns with the World Health Organization's (WHO) definitions of health.

HRQoL models typically consider three key dimensions:

- Physical health
- Mental health
- Social health

2.2.2 Wilson and Cleary's well-validated HRQoL model (1995) conceptualises 'overall quality of life' as the result of the inter-relationships between the different factors below (Bakas et al., 2012; Ojelabi et al., 2017):

- Biological and physiological variables
- Symptom status
- Functional status
- Subjective perception of personal health

2.2.3 While the terms 'quality of life', 'well-being' and 'mental health' are closely related, they are not synonymous. Treating them as identical can lead to over-medicalisation of negative well-being or poor quality of life. Such states may not always stem from illness or mental disorders, but could arise from natural human experiences, such as unhappiness and grief, or external factors such as personal circumstances and environment.

For instance, someone's well-being or quality of life might decline due to inadequate support, rather than the development of a specific mental disorder, such as anxiety or depression. Conversely, a diagnosed mental disorder can reduce well-being and quality of life. In such cases, effective treatment can improve both mental health and well-being.

2.3.0 Mental health, mental ill health, and mental disorders

2.3.1 In clinical settings, when someone is referred for a specific problem, the biomedical approach involves history taking, physical and/or mental state examination, and relevant investigations. The aim of this assessment is to arrive at a diagnosis and formulation. The clinical information collected is compared to established criteria associated with specific mental disorders. These criteria are based on research that identifies which conditions respond to particular interventions.

2.3.2 Different editions of diagnostic manuals, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Disease (ICD) outline the criteria for different mental disorders.

Although mental and behavioural experiences (such as mood) exist on a continuum, these manuals define distinct diagnostic criteria for specific disorders.

Each disorder is characterised as a clinically significant behavioural or psychological pattern or syndrome occurring in an individual. Diagnosis is based on a list of symptoms, where no single symptom is sufficient or always necessary.

To meet diagnostic criteria, the symptoms must be severe enough to cause distress, impair function, or pose an increased risk of death, pain, disability, or loss of freedom, thereby affecting quality of life. Importantly, the pattern must go beyond what is expected or culturally accepted as a typical response to events, such as bereavement.

2.3.3 While the diagnostic approach offers clear benefits and remains an essential component of neuropsychiatric assessment, it has its limitations, especially for people with neurodevelopmental syndromes. The validity, utility, and reliability of diagnostic criteria designed for the typically developing population has been questioned in this context. To address these challenges, modified criteria have been developed for diagnosing mental disorders in people with intellectual disabilities.

Examples include the Diagnostic Manual – Intellectual Disability (DM-ID, see Fletcher et al., 2009) and Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disability/Mental Retardation (DC-LD, see Einfeld, 2003 and Cooper et al., 2003 for detailed discussion).

However, modifying diagnostic criteria carries the risk of altering or diluting established standards, potentially leading to diagnoses of uncertain validity and, consequently, ineffective interventions. Anxiety' or 'anxiousness' affecting people with PWS, as discussed in Part 3, is one such example.

2.3.4 The use of a diagnostic approach is essential for identifying the cause of a child's apparent developmental disability, and for determining whether there is evidence to suggest the child may have a specific syndrome.

Labels such as 'intellectual disability' or 'developmental disability' are often applied to children with neurodevelopmental syndromes but fail to fully reflect the specific nature of the disabilities associated with each syndrome.

Increasingly, research has highlighted that neurodevelopmental syndromes are characterised not only by distinct physical features, but also by unique cognitive and behavioural profiles, and in some cases, specific neuropsychiatric symptoms.

This is particularly true for PWS. Given the potential adverse impact of its neuropsychiatric features, early and accurate diagnosis of PWS is crucial.

2.3.5 In Part 4 of the Report, we explore the factors that influence 'quality of life' and 'well-being'.

However, the mental health of people with PWS is also markedly affected by the impact of an atypical pattern of brain development and the associated intellectual and cognitive impairments.

These factors contribute to what we term 'dimensions of mental ill health', which include specific 'behaviours of concern'. These are considered in detail in Part 3.

2.3.6 The concepts of 'quality of life', 'well-being' and 'mental health' along with definitions of 'mental ill health' and 'mental disorders' are summarised in Table 1.

While these concepts are interconnected, they are distinct, and effectively addressing the mental health needs of people with PWS requires a multidisciplinary and multi-agency approach. For people with PWS not all will be relevant and, for example, some people with PWS may wish to lead a more solitary life.

Also advances in thinking about mental disorders and how they are best conceptualised have challenged the validity of diagnostic categories.

TABLE 1: DEFINITIONS OF WELL-BEING, QUALITY OF LIFE, MENTAL HEALTH AND MENTAL ILL HEALTH

Well-being

Refers to a positive state experienced by a person including:

- A satisfaction with life
- Having the ability to engage with others
- Acknowledging limitations and working with their family and others to reduce their impact
- A sense of worth and of contributing to the family and wider community
- Agency to express one's wants and needs and to act on these

Quality of life

- Refers to different areas of a person's life including economic status, rights, culture and health
- Overall quality of life includes the effects of biological/physiological variables, symptom and functional status, and subjective perceptions of one's own state of health

Mental health

Is more than the absence of mental disorder and is a positive state characterised by the following (see Galderisi et al., 2015):

- The presence of a dynamic internal state or equilibrium
- The ability to maintain harmony in line with universal values
- The ability to recognise, express and modulate emotions
- The ability to cope with adverse events and function socially

Mental ill health

Is a general term used in this Report to refer to the presence of any of the following, if they are singularly or together of sufficient severity to significantly impact a person's life and mental health:

- Impairments in intellectual capacity and social cognition
- The presence of behaviours of concern associated with PWS
- Disturbances in mental state and in mood regulation, including anxiety
- Mental illness

Mental disorders

- Are specific conditions defined in established diagnostic manuals for mental disorder (e.g. affective and bipolar disorders, psychotic illness)
- Their diagnosis usually implies some understanding of causation, and the diagnosis acts as a guide to treatment decisions

Table 1

In Part 2, the scope of the Report has been expanded beyond that of mental health and the presence or absence of a mental disorder to include wider concepts such as 'well-being 'and 'quality of life'. The accepted definitions of these concepts indicate that the needs of people with PWS go beyond a purely physical-health-focused perspective. While access to informed health support is essential, achieving a 'quality of life' and level of 'well-being' comparable to societal norms also requires access to support and to opportunities that enable individuals with PWS and their families to lead fulfilling lives. Strategies for achieving this are discussed in Parts 4 and 5.

Part 3: Behaviours of concern and mental ill health associated with PWS

Introduction

> *I have a lying part in me. When I am asked a question, before I can process the information, I quickly give an answer without thinking. This used to happen more when I was unwell. And it used to happen more when I was more stressed out.*
>
> *It is very frustrating because it makes me stubborn and argumentative.*
>
> *There needs to be a set schedule with food to make me less stressed out.*
>
> Young person with PWS (USA)

3.0.0 Understanding the cognitive, behavioural, and mental health challenges in PWS

3.0.1 The above quote provides an insight into the struggle people with PWS may face and the importance of appropriate and informed support. Meeting the needs of people with PWS is often complex and challenging. A comprehensive approach with an emphasis on both the support environment and the specific characteristics of the individual is required to meet the needs relating to behaviour and/or mental health effectively.

In this part of the Report, we describe and define certain concepts and the particular problems commonly experienced by people with PWS which make up what has been termed the 'cognitive and behavioural phenotype' or 'cognitive and neuropsychiatric' characteristic of PWS.

3.0.2 For many of the behavioural and mental health issues which are listed in Figure 4 and discussed in detail further on, we use the term 'dimension' rather than 'category' to make the point that such mental and behavioural phenomena commonly affecting people with PWS are **neither** just **present nor absent**.

Instead, similar to the mental health of the general population, each is a spectrum varying in degree and intensity between individuals with PWS and within an individual with PWS over time.

In addition, whether or not a particular behaviour of concern is present, and its severity, will be influenced by the environmental circumstances and social context at the time.

3.0.3 Atypical brain development in people with PWS, in contrast to people who have other known genetically determined neurodevelopmental syndromes, is particularly associated with the presence of physiological, behavioural, and endocrinological dysfunction because of impaired development and functioning of the hypothalamus in the brain (Tauber and Höybye, 2021).

In addition, cortical and sub-cortical abnormalities of brain structure are present (see review by Manning et al., 2015), which result, to varying degrees, in the presence of intellectual disabilities and other cognitive and social impairments.

3.0.4 People with PWS also have relative cognitive strengths, an important one being the processing of visual information. For this reason presenting information in picture or written form is often helpful.

Another characteristic which can complicate the assessment of mental health, is a tendency for a person with PWS to confuse reality and fantasy. Stories told by them may be based on things heard from others, from TV or, for example, they may relate to past experiences that are out of context or that happened years ago.

3.0.5 People with PWS differ from each other, like we all do, but having the syndrome is associated with this particular atypical pattern of brain development. It is this that predisposes people with PWS to cognitive and social impairments and to behaviours that have been shown to be particularly common in people with PWS.

The most characteristic of these is an excessive drive to eat (hyperphagia), which can result in excessive food consumption and a high risk of severe and life-threatening obesity.

While hyperphagia is perhaps the best known characteristic of the PWS phenotype there are also other impairments in cognition, behaviour and mental state that can significantly impact the life of a person with PWS and that of their family. These are described below, and the possible causal mechanisms for each are considered in Part 4.

Cognition, Communication and Social Functioning

3.1.0 Overall cognition, communication, and social functioning issues

3.1.1 Typical development results in cognitive, social, and communicative abilities that equip the person for an increasingly independent life. For people with PWS, this development trajectory is atypical and the acquisition of certain cognitive skills and abilities may be delayed, incomplete, or absent.

As we discuss later, the consequence of this is that a person with PWS may have a less-than-optimal understanding of their immediate environment, may struggle to interpret the emotions of others based on the other person's facial expressions or fully be able to anticipate the thoughts and feelings of others.

People with PWS may be less able to empathise with another person's situation in addition to also having difficulty in communicating their own wants, needs and desires. This may lead to a sense of uncertainty and anxiousness, ultimately resulting in actions that are ineffective at maintaining equilibrium.

This inability to effectively respond to social and environmental change can be part of a wider inability to maintain homeostasis in an inevitably changing environment.

As will be discussed in Part 5, this has implications for how people with PWS are best supported and the strategies that might be used to reduce the associated feelings of uncertainty and anxiousness.

3.1.2 The research studies summarised throughout the remainder of Part 3 generally report group findings. However, there is evidence that family, genetic and social backgrounds; access to educational opportunities; and opportunity to continue to use acquired skills will influence the nature and extent of cognitive impairments and whether educational and functional skills are maintained over time (Whittington et al., 2004).

In addition, in one study it has been reported that receiving growth hormone prevented deterioration over time of specific cognitive abilities and also improved abstract reasoning and visuo-spatial skills (Sinnema et al., 2011).

As we discuss, there are also group differences in cognitive profiles dependent on the genetic subtype of PWS. While it is clear that having PWS has a significant impact on cognitive development and subsequent educational and functional abilities, the extent of this varies between people with PWS. Therefore there may be global differences in cognitive profiles depending on what educational and support services are available to children with PWS, a history or not of long-standing severe obesity, and whether or not there is access to growth hormone supplementation.

3.1.3 People with PWS have impairments in general intellectual ability (IQ), executive functions (EF), social cognition, and communication. (Review by Whittington & Holland, 2017).

This means that the distribution of IQ in people with PWS is shifted downwards by approximately 40 points, compared to the mean of 100 in the typically developing population, to 60 in the PWS population.

Scores on IQ are invariably below that expected when considering the person's family, genetic and socio-economic background. In general, research has shown that expressive skills are better than understanding.

3.1.4 There are group differences in mean scores on general intellectual ability between those with PWS due to deletions and those with mUPD. Although people with mUPD have better verbal skills but poorer speed of processing, there is still a considerable overlap in these skills between the two groups. This observed reduction in general ability may be associated with poor educational attainment, particularly in numeracy.

Although general cognitive ability appears to be stable over the lifespan, attainments (such as literacy and numeracy) improve and remain over time providing there is consistent practice (Whittington et al., 2004).

There are also differences in the deletion group, the greater the deletion size the marginally greater the cognitive impairment (Varela et al., 2005).

3.1.5 Executive functions (higher order cognitive control) are impaired in people with PWS compared to the typically developing population.

In particular, deficits in the specific executive function referred to as task-switching (the ability to change attention from one task to another) have been observed and are thought to contribute to a strong preference for routines, resistance to change, and as a consequence an increased likelihood of emotional outbursts (Woodcock et al., 2011). This deficit in task-switching is present regardless of the emotional context associated with the task (Chevalère et al., 2022).

Memory abilities are impaired including that of verbal and visual episodic memory. Planning ability is also impaired, similar to people with other neurodevelopmental syndromes.

Such impairments, although readily detected when using formal cognitive assessments, may be initially hidden and overlooked and may only become apparent to others when it is clear that the person with PWS struggles to learn from their mistakes or to develop appropriate strategies (transformational chains) to achieve a specific goal.

3.1.6 Poor communication skills are a result of a combination of the following:

- **Physical impairments (hypotonia)**, such as articulation difficulties.
- **Impairments in comprehension and vocabulary** that are associated with a lowered general ability.
- **Impairments in social cognition**, such as in theory of mind – these may be linked to the motivation to communicate as well as to misunderstanding of social interactions.
- **Slow processing speed** affects receptive language and conversational skills when in groups, interfering with social relating ability and acquisition of social skills.

3.1.7 Social cognition is impaired in people with PWS relative to the general population. This is loosely linked to impaired general intellectual ability and has been found in investigations of:

- Theory of mind tasks
- Social norms (the Dewey stories)
- Emotion matching of posed faces
- Emotion recognition
- Social attribution of acted scenes played by geometric shapes
- Recognition of sincere and insincere apologies (Whittington and Holland, 2017).

3.1.8 People with PWS have also been shown to score poorly on face/emotion recognition compared to controls. This may contribute to social relationships being difficult, especially in the teenage years.

In addition, those with PWS due to mUPD have an atypical pattern of facial exploration where they look preferentially towards the other person's mouth. In contrast, those with PWS due to a deletion are more attracted to the other person's eye region (Debladis et al., 2019).

3.1.9 While people with PWS may have difficulty interpreting emotions in others, there is a paradox. People with PWS are described as being sensitive to the state of mind of others when they recognise someone is anxious or angry.

While such observations have not been systematically studied, they may be an indication of a general heightened state of alertness associated with a persistent desire for food (see Holland et al., 2022 for discussion).

This may also be true if preoccupied with an idea or action that is emotionally salient for them, not just food.

3.1.10 The above social-cognitive difficulties are evident during early development. Children with the mUPD also have greater difficulties in social cognition that are similar to those observed in children with autism (Dimitropoulous et al., 2022).

How such measures of these specific cognitive impairments and autism characteristics map to impaired social functioning in daily life and impact on mental health is uncertain, but possible implications of these observations are considered in greater detail in subsequent sections.

3.1.11 From a categorical diagnostic perspective, studies have reported that approximately 75% of people with PWS meet the IQ criteria (Full scale IQ<70) necessary for the diagnosis of an Intellectual Developmental Disability (IDD).

This proportion may be less in younger populations of people with PWS as they are likely in some countries to have had the benefits of having been on growth hormone since early childhood.

If there is evidence of associated limitations in the person's abilities (functional impairments) compared to those that would normally be expected for their age, they might then meet the full criteria for IDD.

3.1.12 In some countries, meeting criteria for IDD would enable access to benefits and supports that are provided to people with intellectual disabilities generally. However, when determining the needs of people with PWS, scores on IQ assessments are generally unhelpful.

Functional assessments, such as the Vineland Adaptive Behaviour Scales, are more informative. However, if such functional assessments are undertaken with the person with PWS they may give inaccurate answers, due to their difficulty with self-reflection.

In addition, it is the presence of the above 'hidden' cognitive impairments (such as planning, etc), together with hyperphagia and other dimensions of mental ill health that most impact people's lives and that of their families.

3.1.13 There are similarities between PWS and the characteristics associated with Autistic Spectrum Conditions (ASC). These include: the presence of rituals, restricted interests, and impairments in executive functioning, and social cognition.

In addition, a chromosomal duplication of maternal origin close to the PWS critical region of chromosome 15 is associated with ASC and, rarely, also with psychotic illness. This has been called the Maternal 15q Duplication syndrome (Lusk et al., 2016).

This observation led to the hypothesis that those with PWS from the mUPD genotype, but not the deletion genotype, would be at risk for autism and psychosis (Veltman et al., 2005).

3.1.14 Studies comparing people with PWS and those with diagnosed ASC have found both similarities and differences in autistic characteristics, implying that the two conditions differ but overlap in some features.

Use of the Autism Diagnostic Observation Schedule (ADOS) to assess autism in people with PWS has been extensive, giving rise to what are generally considered to be improbably high estimates of prevalence. In a systematic review (Bennett et al., 2015), 18% of those with the deletion form of PWS and 35% with mUPD were reported to meet such criteria.

Probably the best estimate to date of the prevalence of an ASC in people with PWS is from Dykens et al. (2017), who found 12.3% of their sample to have an autistic spectrum condition, and incidentally showed the predictive value of the ADOS to be poor (56%).

Insistence on sameness in routines and events, and compulsivity were seen in 76 to 100% of this sample. However, people with PWS who received a diagnosis of autism showed more difficulty with overall rapport and reduced quality in their responses and overtures to others.

3.1.15 The similarities between ASC and PWS could indicate that there is a similar pattern of atypical brain development. However, PWS also significantly differs from ASC in its additional phenotypic manifestations, such as the early hypotonia, relative growth and sex hormone deficiencies, and the development of hyperphagia, indicating that other areas of brain development are affected in people with PWS and not in people with autism, most strikingly the hypothalamus.

Families report that, where their child has received either a formal diagnosis of Intellectual Developmental Disabilities and/or an Autistic Spectrum Condition, it usually enables access to additional services and extra benefits and may also inform educational support.

People with PWS who do not meet the additional criteria for autistic disorder may still benefit from the perspectives and expertise of specialists supporting people with an autistic spectrum condition as well as from PWS-specific and any other support that may be available.

People with PWS have, to varying degrees, intellectual and cognitive impairments, and specific developmental, cognitive and behavioural characteristics. These may overlap with the accepted criteria for Intellectual Developmental Disabilities and/or Autistic Spectrum Conditions as set out in diagnostic manuals such as ICD-11 and DSM-V.

In some countries, people with PWS are denied access to services for people with intellectual disabilities or autistic spectrum conditions if they do not formally meet the necessary criteria, even though the services may be appropriate and the person would benefit. Families and clinicians should work together to challenge overly rigid interpretations of such inclusion criteria.

3.2.0 Repetitive and ritualistic behaviours, rigidity and perseveration, and associated behaviours

3.2.1 Repetitive and ritualistic behaviours, together with rigidity and perseveration, are well described in people with PWS.

Typically developing children often go through a phase of ritualistic, repetitive and obsessive behaviours, such as repetitive questioning, insisting on bedtime routines, avoiding cracks when walking on paving stones, or obsessively collecting particular items. These behaviours may begin very early and persist into adolescence before diminishing.

In people with PWS, however, such repetitive and ritualistic behaviours often persist throughout the lifespan and are recognised as part of the PWS phenotype. Strong, focused interests described as 'intense obsessionality' are also characteristic of people with PWS (Bechis et al., 2021).

Although most people with PWS have repetitive and ritualistic behaviours and interests, the frequency, severity, developmental trajectory, and overall impact on the person's life varies. When these behaviours are coupled with significant social communication difficulties, they may be indicative of a co-morbid Autistic Spectrum Condition (as discussed further in this section).

3.2.2 The types of repetitive and ritualistic behaviours seen include:

- Insistence on maintaining rigid routines
- Restricted interests
- Excessive repetition of preferred activities
- Perseveration
- Things being ordered in a particular way
- Hoarding
- Propensity to repetitively ask questions
- Seeking reassurance
- Repeating the same phrase/statement

(see Bédard et al., 2020, Clarke et al., 2002, Haig & Woodcock, 2017,, Whittington et al., 2010, Wigren & Hansen, 2003, Woodcock et al., 2009.)

3.2.3 Individuals with PWS may insist that routines and tasks are completed in a specific way, such as following a particular sequence when getting dressed or insisting on eating with a specific plate and spoon.

This may extend beyond their own behaviour to include demanding that others behave in a specific way; such as insisting someone wears particular clothes or sits in a particular place at the table.

Additionally, it may be difficult for people with PWS to move beyond routines or tasks that are not completed to their specifications.

3.2.4 Deviations from routines or other preferences may result in persistent perseveration that is difficult to interrupt or redirect and which can escalate to arguing and emotional outbursts.

Perseveration is the involuntary repetition of a behaviour, speech, or thought, even when there is no stimulus present. Perseveration extends past routines and can include specific behaviours at mealtimes, gaining access to preferred items or activities, and access to particular people.

Perseveration may take the form of repetitive asking and telling and can escalate to emotional outbursts if questions go unanswered, access is denied, or the expected response does not occur.

3.2.5 In the PWS literature, repetitive and ritualistic behaviours and interests have been interpreted as a manifestation of obsessive-compulsive disorder (OCD), largely based on the use of the Yale-Brown Obsessive-Compulsive Scale (YBOCS).

This scale was developed for the general population rather than for those with developmental intellectual impairments.

People in the general population with OCD find their obsessions aversive, whereas most people with PWS do not view their obsessions as unpleasant and generally do not wish to alter them.

3.2.6 Another aspect of these particular behaviours is the need for routine. This has been linked to executive function impairments and to emotional outbursts in the context of unexpected change (Woodcock et al., 2009), which again distinguishes them from OCD.

A factor analysis of such behaviours in people with diagnosed OCD in the typically developing population produced three factors:

- Hoarding/symmetry
- Contamination/cleaning
- Pure obsessions (Baer, 1993).

In contrast, in people with PWS the loading was on hoarding symptomatology alone (Feurer et al., 1998). Therefore, given these different strands of evidence, from a diagnostic perspective, most people with PWS would not be considered to meet the diagnostic criteria for OCD.

3.2.7 The behaviours observed, such as hoarding, the need to ask or tell, and insistence on routine, are like those that are seen in early development in typically developing children (Evans et al., 1997).

These are also like those seen in people with other developmental disabilities, such as Autism Spectrum Condition (ASC), rather than the behaviours seen in OCD (Greaves et al., 2006, Whittington et al., 2010, Wigren & Hansen, 2003, Woodcock et al., 2009).

Despite similarities between the repetitive and ritualistic behaviours in ASC and PWS, the types of behaviours exhibited by each population are different. Children with PWS are more likely to engage in repetitive asking and telling, as well as in collecting and storing objects, while children with ASC are more likely to demonstrate food selectivity and hyper-awareness of environmental variables, such as the placement or order of objects, or other inconsistencies (Greaves et al., 2006).

3.2.8 'Oppositional behaviour' often takes the form of arguments and refusals, impulsively declining to accept an item or engage in an activity, only to immediately change their mind. Individuals may firmly refuse either verbally or by escalating to an emotional outburst, if pushed to do something they do not want to do, or in a way they do not want to do it.

These types of situations may result in confrontations, with the person with PWS arguing a particular point even in the presence of clear evidence to the contrary.

Also, individuals may appear to ignore a request or demand, but this behaviour may be due to processing speed delay that impacts both understanding and responding in a timely fashion. This behaviour may be labelled as oppositional and escalate, however, waiting the person out may result in compliance albeit rather delayed.

3.2.9 Rigidity, perseveration and confabulation underlie the insistence on routines and a person's performance on cognitive tasks, such as a verbal fluency.

Perseveration can also lead to repetitive questioning or statements. These behaviours, often expressed as repeated "why?" questions, are a normal part of childhood development and may serve as a coping mechanism for managing anxiety related to uncertainty.

However, in people with PWS it persists into adulthood and becomes more varied. Rigidity, perseveration and confabulation may be more marked when the person with PWS does not understand the situation. It also underlies the impairment in task-shifting abilities, something commonly observed in people with PWS.

3.2.10 Although this has not been systematically investigated, there are reports of people with PWS complaining of specific sensory sensitivities including dislike of particular odours, or particular colours or noises inducing sensory discomfort. Such sensitivities may be part of a general heightened awareness and inability to adapt to environmental stimuli.

This is often also a trait in people with an Autism Spectrum Condition.

3.2.11 A behaviour that has not been studied in any detail, but which is reported and potentially very serious is that of running away (absconding, eloping). This may be during the night when others are unaware or done suddenly and apparently spontaneously during the day.

How such behaviour is best understood and whether it is a manifestation of other PWS-associated traits, such as anxiousness, impulsivity, or oppositional behaviour, is unknown. It may be driven by a particularly strong desire to seek out food or any other salient reward. A poor understanding of time, distance, or risk may also contribute to the sometimes-reckless nature of the behaviour.

Possibly related to running away, panic reactions have been described in people with PWS under circumstances where food is seen by them but access to it is not allowed. Such behaviour may particularly occur where that person believed at that time that access to food should have been allowed.

Running away behaviour understandably causes concern among those providing support and has been known to lead to the death of someone with PWS who was hit by a car (see paper by Murray et al., 2021). The management of this behaviour will be considered in Part 4.

Repetitive and ritualistic behaviours, rigidity, perseveration, confabulation, and oppositional behaviours are commonly described in people with PWS. These may be similar to behaviours seen in early childhood in typically developing children and may also be similar to but not identical to behaviours that are observed in people with autism spectrum conditions.

The above behaviours are different from and do not meet the diagnostic criteria for obsessive-compulsive disorder (OCD) as it is observed in the typically developing population.

The above behavioural traits in a person with PWS may in specific situations contribute to the occurrence of emotional outbursts, particularly when, for example, routines are interrupted.

> *"You can never tell him anything, he knows everything. There is nothing on this earth that he doesn't know. It doesn't matter what it is, for example at school when you say 'a cat is not spelt with a K it's spelt with a C', he will say 'no' and that time he will spell it the way he wants. When he finally decides to change it, he will. It's one of the things that his teachers are struggling with."*
>
> Mother of a schoolboy with PWS (South Africa)

Behaviours of concern

3.3.0 Overall behaviours of concern

3.3.1 Studies using different methodologies and scales, such as the Child Behaviour Checklist (CBCL) and the Developmental Behaviour Checklist (DBC), have described what has become known as the 'behavioural' or 'neuropsychiatric' phenotype of PWS.

Papers have reported findings from clinical and population-based cohorts of children and adults with PWS from different countries (Dykens et al., 2003, Einfeld et al., 1999, Holland et al., 2003, Schwartz et al., 2021, Sinnema et al., 2011).

The terminology used and the exact percentages reported vary between studies. However, there is strong agreement that those listed in **Figure 4** are the main components, together with abnormal affective states and what is described as 'anxiety'. As we discuss later, 'anxiety' may be better referred to as 'anxiousness'.

3.3.2 Studies using the Developmental Behaviour Checklist (DBC) that followed a cohort of children and adults with PWS, and also other groups with different neurodevelopmental syndromes, have shown that these characteristics, although not unique to PWS, have a high prevalence, and are persistent over time (Einfeld et al., 1999).

As is considered further in Part 4 on mechanisms, the implication of such observations is that there must be a link between the PWS genotype and this characteristic PWS neuropsychiatric phenotype.

In the following sections, we summarise the main characteristics of these 'behaviours of concern' and 'abnormal mental states' with particular reference to the paper by Schwartz et al., 2021.

3.4.0 Hyperphagia (drive to eat)

3.4.1 People with PWS have an abnormality in the part of their brain (the hypothalamus) that determines, through activation of different brain networks and cortical regions, the presence of feelings of hunger before, and the onset of a sense of satiety after eating.

There remains a debate as to whether people with PWS experience a continuous sense of hunger even after eating but it is clear that they have this continuous urge to eat.

This behaviour of hyperphagia is very different from the period of poor eating in the early years. This drive to eat leads to the characteristic pattern of excessive food intake that becomes apparent during early childhood if the child with PWS has free access to food. Children and adults with PWS are unable to limit their calorie intake in line with their energy needs.

At birth, infants with PWS are below weight for their gestational age, have a poor suck and are unable or reluctant to feed, and fail to thrive . Only with tube feeding in these early years is the necessary growth and weight gain possible.

In one study, mothers reported that their infants with PWS first developed an interest in food as early as 30 months (Goldstone et al., 2012).

Different stages from hypophagia to hyperphagia have been described from the early phase of failure to thrive, to weight increase in the apparent absence of over-eating, to the onset of hyperphagia at an average age of eight years (Miller et al., 2011).

The risks associated with hyperphagia remain lifelong if access to food is not carefully managed. The underlying mechanisms and approaches to intervention are considered in Parts 4 and 5 of the Report.

3.4.2 The over-eating and apparent on-going drive to eat occurs to varying degrees in close to 100% of people with PWS. The central characteristic of hyperphagia is the continuing ingestion of food significantly beyond the amount required to meet energy needs.

Studies using the hyperphagia questionnaire have highlighted other related behaviours including:

- Hoarding and stealing food
- Pre-occupation with and excessive talking about food
- The eating of food that would normally be considered inedible (Schwartz et al., 2021).

3.4.3 Studies involving the direct observations of eating behaviour when having access to food, usually for a period of up to one hour, have shown excessive food intake, with the majority of people with PWS continuing to eat well after those in any control group stopped (Holland et al., 1993, Lindgren et al., 2000, Zipf & Bernston, 1987).

Ratings of the level of hunger and fullness by people with PWS during food intake have been reported to change in the expected direction when eating, but only after a calorie intake that is three times that of typically developing people (Holland et al., 1993).

The findings from these observational studies have suggested that the feedback mechanisms that result in satiation are insensitive but not completely absent.

3.4.4 The younger generation of children with PWS who have had a diagnosis early in life and who have some understanding of their condition may be able to exercise some control over food intake in the short term. This may continue up to a certain age while living within environments where there are food controls in place. However, long-term access to unrestricted food typically leads to significant and potentially life-threatening levels of weight gain.

This is not due to a lack of willpower on their part but is a result of the unique PWS genotype which affects brain development and disrupts the brain mechanisms that regulate satiety and energy balance (see Part 4).

It remains uncertain whether people with PWS can be helped to acquire some partial control over food intake, but anecdotal reports of the observance of fasts for religious reasons, such as during Ramadan, suggests that under the right circumstances and for fixed periods of time it is possible.

Loss of appetite may occur with serious illness, which may not be obvious to others at the time. However, the presence of such an underlying physical illness is unlikely if the person with PWS is clearly willing to, and agrees to fast, he/she does not complain, and no abnormal physical symptoms are seen.

As discussed in Part 5, without there being treatments that reduce hyperphagia, managing the food environment through food security (see later in the Report's description of food security) remains the recommended approach to prevent the onset of life-threatening obesity.

3.4.5 The intensity of hyperphagia varies between individuals with PWS and may vary in an individual over time. However, because of severe obesity, or because of choking and related problems, hyperphagia is associated with increased morbidity and mortality, and shortened life expectancy for people with PWS (Bellis et al., 2021).

At its most extreme hyperphagia can result in acute gastric distension and stomach rupture.

The risk of hyperphagia is universal in people with PWS. The severity varies, but in the absence of appropriate management it will result in severe obesity, impacting on well-being, mental and physical health and can significantly reduce life-expectancy.

People with PWS are unable to match their energy intake in line with their energy needs. At birth and during early childhood, energy intake would be below what is required unless additional methods of feeding are used. However, from early childhood, people with PWS have a severely impaired ability to limit the amount they eat in accordance to their energy needs.

People with PWS, through no fault of their own, have an impaired sense of the feelings of hunger and fullness during and following food intake, which results in an ongoing desire to eat after energy needs are met (see Part 5 for intervention).

3.5.0 Emotional (temper) outbursts

3.5.1 'Emotional (temper) outbursts' is the term used to describe a characteristic pattern of behaviours that are usually of relatively rapid onset and last for a period of time before resolving. Such outbursts are characteristic of early development in all children (including typically developing children) until around six years of age, however, for people with PWS there is an increased risk for emotional outbursts into later childhood and adult life.

> *"Anger is one of the biggest problems, he gets obsessively angry, like uncontrollably angry… 'I don't like you, I hate you', all those things, 'you don't talk to me'. If it is his aunt, he says 'you are no longer my aunt.'"*
>
> Mother of a schoolboy with PWS (South Africa)

> *"Sometimes my mind rushes. I have many thoughts in my head and I am unable to focus on one. I try to explain myself to others but they don't seem to understand or sometimes even don't listen. That makes me really angry. In this moment it helps me a lot, when someone is just there for me, perhaps touches my hand and helps me focus on one thing, that is important right now."*
>
> Young man with PWS (Germany)

3.5.2 Emotional outbursts have been reported in 60 – 70% of people with PWS across all ages and genetic types of PWS.

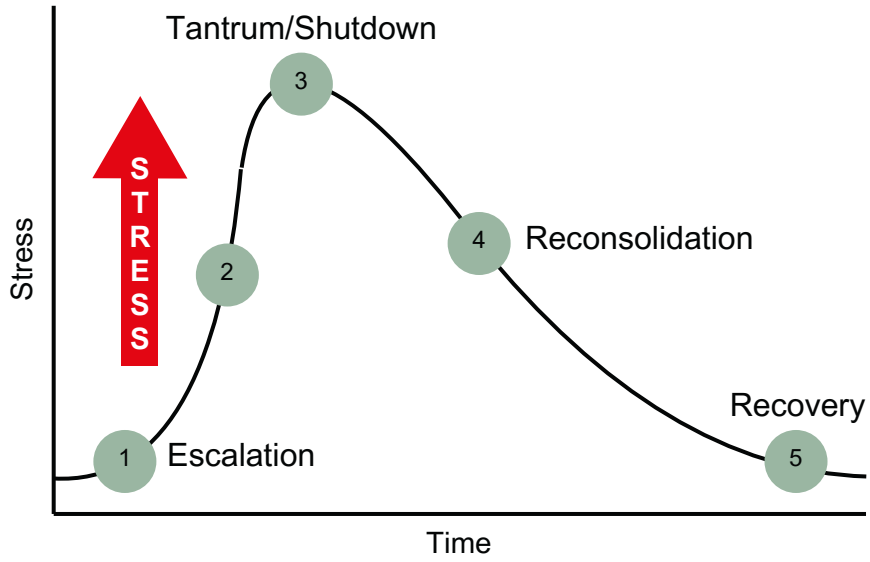
The outbursts usually have a characteristic pattern to their onset and subsequent course in a particular individual, often triggered by some relatively minor change, for example, a perceived insult, a disagreement over food, or a demand, or a triggered memory of a previous grievance or stressful situation.

The outbursts may start with repetitive questioning, and build up to more aggressive behaviour, such as shouting, crying and yelling, and sometimes physical aggression, before resolving after minutes or even hours, followed by scenes of emotional distress and apologies, and ending in exhaustion.

While it may be possible to defuse the situation early on through distraction, there comes a point when the outburst must take its course (Rice et al., 2018, Tunnicliffe et al., 2014).

3.5.3 This pattern is illustrated in **Figure 6**. However, the peak of such outbursts can be longer and the buildup may not be as rapid as indicated in the diagram, particularly when low levels of stressors are adding to the emotional load over time. The possible mechanisms and treatments will be covered in Part 4.

ANATOMY OF A TANTRUM



KEY:
1- Escalation phase; stress is increasing, but interventions may de-escalate the situation.
2- Stress effects are causing a major change in the brain and behaviour. The person is no longer responsive to verbal or physical redirection, and the tantrum is imminent.
3- The tantrum or shut down; this is a massive discharge of neurochemical and physical energy of variable duration for each person, but it is always time limited.
4- Reconsolidation; this phase is gradual because it takes time for the sympathetic nervous system to come back 'on-line'.
5- Recovery phase with return to baseline.

Figure 6 An illustration of the characteristic time course of an emotional outburst. Courtesy of Janice Forster.

Emotional outbursts are very common, and their occurrence can have a serious impact on the subjective well-being and quality of life of the individual with PWS, and that of their family.

3.6.0 Body-focussed self-harming behaviours

3.6.1 Body-focused self-harming behaviours of various forms are prevalent in people with intellectual disabilities, particularly those with severe or profound intellectual disabilities and autism.

There may also be specificity between the cause of a person's developmental disability and particular forms of self-harming behaviour (see Waite et al., 2014 for a discussion of behavioural phenotypes in different genetic neurodevelopmental syndromes).

Because of the specificity of the form of self-harm across genetic syndromes, self-harm is not thought to be primarily a learned behaviour, but rather it is determined by the biology associated with that specific syndrome.

This specificity is observed in people with PWS where skin picking and to a lesser extent rectal picking are the most prevalent form of self-harming behaviour.

Skin picking is reported to occur in 50% to 100% of cases and across ages, sometimes with onset as early as three years old (Bull et al., 2021, Whittington & Holland, 2020).

3.6.2 Skin picking may start at the site of a pre-existing lesion (e.g. scar or insect bite), although this is not invariably the case, and most commonly involves the arms, legs, and face.

In a report of interviews, ten people with PWS were asked why they skin picked. Most said itchy skin, and others said boredom or anxiety (Didden et al., 2008.)

At its most severe, persistent skin picking can result in severe skin ulceration and tissue damage requiring medical treatment and sometimes hospitalisation.

3.6.3 While this specific form of body-focussed self-harming behaviour must arise as a consequence of a PWS-related biological vulnerability, is also clear that the frequency of occurrence of such behaviours is also dependent on environmental circumstances, such as lack of structure and activity, and may also be influenced by specific contingencies (Hall et al., 2014).

Particularly if an existing tendency to skin pick becomes worse, or skin picking or some other form of self-harming behaviour occurs for the first time, an explanation for this is required. This will be considered later under mechanisms (Part 4) and in the treatment section in Part 5.

3.6.4 A comprehensive review of skin-picking in PWS concluded that:

- Skin picking occurs in the general population, but in PWS the propensity to skin pick is vastly increased, due to a shift downwards in the risk threshold.
- The behaviour often, but not always, starts where there is an insect bite or lesion and then persists over time.
- The time course may be episodic, often worse during seasons when there is exposed skin and when insect bites occur. It may diminish with multimodal treatment, and remain in remission until the next cycle.
- It may be maintained over time by setting up an inflammatory response that needs to be relieved and the presence of a high pain threshold (with which it is correlated) that makes skin or rectal picking less aversive.
- Or, it may be maintained because of self-soothing properties associated with repetitive behaviours that are automatically reinforced.

- It is not part of the obsessive-compulsive cluster of symptoms, but it may be related to stress, anxiety and low mood when the intensity of the self-harming behaviour is more severe.

3.6.5 Rectal picking is another form of self-harming behaviour, and although this has not been systematically studied, it is considered to be a more severe extension of skin picking.

Case reports (Butler, 2021) and clinical experiences indicate that it can be severe enough to be associated with considerable bleeding and anemia, and can cause damage to the rectum. This behaviour may also be associated with the insertion of objects into the rectum.

As with skin picking it is persistent and can lead to those with PWS spending lengthy periods of time in the toilet. Factors that may increase the risk include severe constipation and the feeling that stool is stuck in the rectum.

Rectal prolapse may be an aggravating factor as well as potential a consequence of severe rectal picking. Bleeding may occur and lead to unnecessary medical investigation for colitis.

Rectal picking is more common among those with maternal UPD form of PWS.

3.6.6 Hair pulling (trichotillomania) is also reported but this seems no more prevalent than in the general population. This may include eating the hair, which cannot then be digested and may result in gastro-intestinal complications, and potentially a gastrointestinal blockage.

Body-focused self-harming behaviour, usually in the form of persistent skin picking, is very common. Less commonly it may be associated with rectal picking. These behaviours can be disfiguring and are associated with significant tissue damage and risk of serious infection and medical morbidity.

Hyperphagia, emotional outbursts, and skin picking are not unique to PWS, but their frequent occurrence and particular characteristics are specific to PWS. The occurrence of these different behaviours both singularly and together give rise to the biggest challenges for people with PWS themselves, and their families, and can impact profoundly on well-being and quality of life.

Abnormalities of mental state

3.7.0 Overall abnormalities of mental state

3.7.1 In addition to the behaviours of concern already discussed, people with PWS have an increased risk for the occurrence of disorders that are primarily characterised by changes in subjective feelings (their mental state), such as affective (mood) disorders, anxiousness, and the occurrence of mental beliefs and experiences considered indicative of a psychotic illness.

These changes in a person's mental state may also be associated with the onset of new unusual behaviours or deterioration in existing behaviours.

If a careful history that asks the person about their mood and mental experiences is not taken, the presence of these problems can be missed (see Part 4).

A detailed assessment identifying the presence or not of a co-morbid mental illness is important to provide direction for effective treatment.

We describe the common abnormalities of mental state that have been reported in this Part and consider the reasons for this and their treatments later in the Report in Parts 4 and 5.

The clinical phenomena that have been understood to indicate anxiety in people with PWS include:

- Repetitive questioning
- Pacing
- Excessive talking
- Hand movements
- Trembling
- Checking behaviours

However, some of these are symptoms that are recognised as also being common in people with PWS, independent of any anxiety disorder.

In addition, people with PWS may have difficulty describing internal mental states, such as feelings of apprehension, as well as physical symptoms associated with anxiety and increased autonomic arousal, which are often considered supporting characteristics in standard diagnostic criteria. A heightened awareness or alertness of specific details in their environment is also described.

Other symptoms, such as sweating, palpitations, and gastrointestinal phenomena, may not be present. This may be because what is described as anxiety in people with PWS is etiologically different or because these symptoms do not manifest in people with PWS, due to autonomic nervous system dysfunction.

3.7.3 As will be discussed later, 'anxiety' symptoms (anxiousness), repetitive questioning and the occurrence of outbursts may be related, particularly in the context of uncertainty and the need to switch attention from one task to another.

For people with PWS the cognitive demand associated with such change may be particularly high, giving rise to increased stress in that moment, with the subsequent onset of repetitive questioning occurring as a coping strategy (Woodcock et al., 2009).

It may also be the case, given the cognitive impairments and impaired hypothalamic functioning associated with PWS, that people with PWS are unable to accurately interpret their social and physical environment (see section on atypical brain development).

This impaired perception and understanding of the environment might in turn result in an increased internal sense of uncertainty and an inability to respond effectively to actual or perceived risks of harm, therefore leading to a sense of fear. Anticipatory anxiety may also occur because of such uncertainties, prior to meal times or to some expected event.

Anxiousness in people with PWS may well be situational and related, for example, to some change in routine or uncertainty around food.

Anxiousness in a person with PWS may be more a consequence of a feeling of uncertainty than is the case with generalised anxiety symptoms in the typically developing population.

Clinicians should be guided by the relationship of 'anxiety symptoms' to change, i.e., what was the person expecting, and their severity and persistence over time when considering treatment (see Part 4 on assessment and treatment).

3.8.0 Affective and psychotic illnesses

3.8.1 Affective and psychotic illnesses are relatively common among people with PWS. Affective illnesses include depression and bipolar disorder.

Persons with depression experience pervasive feelings of deep sadness along with hopelessness, changes in their sleep and/or appetite, low energy, low interest, difficulty concentrating, guilty preoccupations, paranoia, and suicidal ideations.

Extreme mood swings characteristic of bipolar disorder (formerly called manic-depressive illness) may also be observed. During the manic phase, the person may have an abnormally elevated mood and/or exhibit prolonged irritability along with high energy, increased goal-directed activity, and decreased need for sleep, beliefs (delusions) that they can do things they cannot, as well as poor decision-making ability.

Psychotic features may accompany both depression and bipolar disorder. Psychosis is a condition where the person may be losing contact with reality and their thoughts or perception may be altered, such that they may have false beliefs, delusions, or experience auditory, visual, or tactile hallucinations.

3.8.2 In the general population, prevalence rates of depression, bipolar disorder, and psychosis are estimated to be about 10%, 5%, and 0.5%, respectively (Lai et al., 2019). However, in people with PWS, rates of affective and psychotic disorders appear much higher than the general population.

For example, a recent study of the Global Prader-Willi Syndrome Registry of 750 individuals with PWS found 13.2%, 6.9%, and 8.3% reportedly had a diagnosis of depression, bipolar disorder, or psychotic disorder (Peleggi et al., 2021).

Another study of a cohort of 119 individuals with genetically confirmed PWS found that 38.7% of the cohort had had one or more affective or psychotic illnesses (Soni et al., 2007, 2008). This sample was followed up 2.5 years after initial screening, which revealed that those with mUPD were at increased risk for recurrence, a more severe course of illness, and poorer responses to treatment than those with deletion.

Interestingly, the deletion type was found to be associated with non-psychotic depressive illnesses, whereas mUPD was associated with bipolar disorder with psychotic symptoms.

3.8.3 Notably, several case studies have reported atypical presentation of affective and psychotic illnesses in people with PWS.

A recent systematic review of symptoms of psychosis in cohort studies or case reports of people with PWS has described a distinct psychiatric condition. The main characteristics are:

- An acute onset
- A brief duration (usually a few weeks)
- Prominent co-occurring anxiety
- Affective instability or dysphoric mood
- Psychotic symptoms, such as delusional ideation and/or hallucination, which may be also accompanied by changes in motility and decreased oral intake (Aman et al., 2024, Singh et al., 2019, Verhoeven et al., 2003).

These phenomena do not fit well with the specific diagnostic characteristics of affective or psychotic disorder diagnoses, such as bipolar disorder, schizophrenia, or schizoaffective disorder.

Rather, PWS experts have used a concept called cycloid psychosis (acute psychotic episodes that are followed by periods of full remission) or cycloid psychotic disorder to capture these affective and psychotic episodes seen among persons with PWS.

The majority of people with PWS presenting with cycloid psychosis phenomenology reportedly had previous diagnoses of depression, bipolar, or psychotic disorders and are more likely to have mUPD type (Singh et al., 2018, Verhoeven et al., 2003).

This relationship between an increased risk of psychosis and the presence of PWS due to a mUPD was first observed by Boer et al. (2002) and has been subsequently reported in several further studies (see Aman et al., 2024).

3.8.4 In the typically developing population and for people with PWS the risk for developing an affective disorder and/or psychotic illness begins to increase in the teenage years.

For people with PWS this increased propensity to such illnesses with age may have a serious impact at school and at the time of transition into adult life.

During this time, increased demands and expectations, along with the shift from the structured school environment to a lack of meaningful activity as an adult can pose serious challenges. At such times families are often faced with uncertainty as to the reasons for the marked deterioration in their child's behaviour, and are therefore unclear as to how to respond.

In the absence of any proper assessment and diagnosis, a rational and informed treatment plan is never developed and there may be an increased risk of self-harm or of others being harmed because of the behaviour.

> *"When my daughter had acute psychosis, it was obvious to me that her behaviour was very out of the ordinary. Unfortunately, to professionals who were caring for her at that time, it just seemed like a characteristic of a learning disability – they had no prior knowledge of what she had been like before the psychosis."*
>
> Mother of a young woman with PWS (UK)

3.8.5 Suicidal Ideation and behaviours in people with PWS can be a concern, especially in a subset of individuals with PWS. A published review (Peleggi et al., 2021) of caregiver reported data from a large number of participants (N=750) in the Global PWS Registry found that 12.5% (N=94) reported a history of suicidal ideation (SI) and 3.3 % (N= 24) reported a history of at least one suicide attempt (SA) by the person with PWS.

Suicidal ideation is the presence of thoughts or talk about wanting to harm/kill oneself. Those with PWS often use these types of statements because they have learnt that they have a particular effect on their caregivers and ultimately on their immediate environment. They may wish to gain attention, avoid circumstances that they perceive as aversive, or control a particular situation when very angry or upset.

It is very important to obtain information that can help determine the motivation and enable an understanding of the environmental stressors that trigger such statements.

Of those who had attempted suicide, there was a smaller sub-group who had made multiple suicide attempts. This subgroup is at particularly high risk and requires close monitoring. The mean age of onset for the first suicide attempt was 16.25 years.

Factors associated with suicidal ideation and behaviours appear to be older age of the person with PWS, male gender, history of aggressive behaviours (such as emotional outbursts), and mental health/psychiatric problems.

As is seen in other populations, psychiatric family history also increases suicide risk in a person with PWS.

Additionally, given the close involvement of caregivers in the lives of many people with PWS, assessment of such risk should include information from caregivers who may be able to better describe the circumstances and help to determine if the person with PWS is at risk of suicide.

PWS is associated with increased rates of mood instability, affective disorders, and psychotic illnesses presenting with changes in, or the onset of, abnormal behaviours and evidence of an abnormal mental state.

Presentations of mental illness may be atypical, not always fitting well to traditional diagnostic criteria, such as those for bipolar disorder or schizophrenia.

Cycloid Psychosis, a brief psychosis with strong affective components, is closest in characteristics to the psychosis seen in most people with PWS.

Having the mUPD genetic type of PWS confers an increased risk to psychotic illnesses compared to those with 15q11-13 deletions.

Suicidal ideation may occur and a proportion of people with PWS are at risk for attempting suicide.

PERSONAL INSIGHT WRITTEN SPECIFICALLY FOR THIS REPORT

I was born with PWS and as I grow up I gained schizophrenia due to the chemical imbalance in my brain. So I decided to write this paper to educate people with PWS or their carers on what to look out for when comes to mental illnesses and the syndrome.

PSYCHOSIS

Is when you might do something you might not usually do. Like you might become violent, you may walk around in your birthday suit. You may eat food that you may not usually eat. You might not sleep very well, and you might more inclined to have an argument. Also you may not remember what you have done due to psychosis. You might walk off on the street at anytime of the day, without telling anyone where you're going.

WHAT TO LOOK OUT FOR

You might feel heightened or agitated - You might feel worried but not know why - You might start to eat to for comfort, You might walk around naked - You might start shouting at people within your home - You might have had something go missing but think someone took it. Lack of sleep. You might have bold eyes, not able to stand up straight.

These scenarios are what to look out for at the start of psychosis. For me these scenarios I have experienced when I started to go through psychosis.

SUPPORTIVE PEOPLE

Could call the psych team with the ambulance, to see if your mental health needs more of hospital stay to get yourself feeling normal again. If you have already been to hospital you might have a CAT team to call to get assessed. You might have list of things you might associate with your mental health (I have a check list). A supportive person can help with that so you might get on top of it before a big psychosis or mental health breakdown.

MY MENTAL HEALTH EXPERIENCE

Experience with emergency personal (police or hospital people) - I have had mixed experiences where I may think I'm fine and I am yet the hospital may think I'm not ok. But then they come to my house and understand my point of view

PSYCHIATRIC WARDS

I have had many different experiences with wards. My last experienced was much better as I got a different doctor from last time and he could see what made me want to come to hospital and the situation was assessed and I got the treatment needed.

PWS is so rare that sometimes people might not really understand when issues are different; like I went to hospital for constipation but the hospital staff thought I was going through psychosis and I had too much to eat. But that was not the case, so when I discharged I got information for my GP so I could get help with my constipation. Then when I needed to go to hospital again this time for a breakdown, the doctor that saw me asked me what was wrong and could see that I was having real issue with my mental health.

Young man with PWS (Australia)

The severity of these different behaviours of concern or dimensions of mental ill health described in Part 3 should be considered from a developmental perspective with there being at-risk periods during development. For example, hyperphagia becomes apparent early in childhood as do emotional outbursts and the risk of mood disorders and of psychotic illness may increase in the teenage period.

In addition the propensity to, and likelihood of, each of the above may be best understood as arising as a consequence of the following:

- Interactions between environmental factors and development-related biological vulnerabilities typical of PWS, particularly the effects of impaired hypothalamic development (Brown et al., 2022).

- The impact of atypical brain development on cognitive development and abilities, including impaired cognitive flexibility, deficits in executive function, and impairments in social cognition.

- The modifying influences of individual factors, early life experiences, and the social and environmental context.

The characterisation of the cognitive and neuropsychiatric phenotype of PWS has led to research seeking to identify possible causal mechanisms so as to inform treatment development. In Part 4 our understanding of the above phenotypes are considered and in Part 5 approaches to prevention and treatment are discussed.

Part 4: Mechanisms of well-being and mental ill health

Introduction

4.0.0 Understanding determinants and mechanisms of well-being and mental health in PWS

4.0.1 The aims of Part 4 are to consider:

- The determinants of well-being, quality of life, and mental health in children and adults with PWS.
- The underlying causal mechanisms that may result in particular behaviours of concern or mental ill health associated with PWS.

This Part explores the factors that may explain the behaviours and mental health patterns associated with PWS. The terms 'determinants' and 'mechanisms' are used here to describe the developmental, biological, psychological, or environmental (social) factors that research indicates, or hypothesises, are causally related to maintaining well-being, quality of life, and mental health, or are associated with the occurrence of behaviours of concern or mental ill-health in people with PWS.

Understanding these factors guides the implementation of existing interventions and informs the development of new treatments.

4.0.2 During the meetings of the Mental Health Network, it became clear that clinical and social care practices vary, influenced by professional discipline and the training and theoretical perspectives prominent in the different countries.

Individual clinicians, for example, might approach their practice primarily from a psychoanalytical, developmental, biomedical, systemic, or behavioural perspective.

Regardless of differences in perspective, we identified three broad principles that informed our thinking.

These are discussed in greater detail later in Part 4.

In summary, these are:

1. **Systemic support and family impact:** The importance of having a systemic perspective, recognising the central importance of the support environment, such as that provided by the family, professional carers, or the wider community. The emotional, social, financial, and physical resources of their families will influence the well-being, quality of life, and mental health of individuals with PWS. In addition, the mental health and well-being of the person with PWS will impact on the family.

2. **Genetic basis and neuropsychiatric profile:** PWS is fundamentally a genetically-determined syndrome associated with atypical brain development, intellectual and cognitive impairments, and an increased risk for the development of specific behaviours of concern and mental ill health. These have been described earlier in the Report and have been referred to as 'the cognitive and neuropsychiatric phenotype' of PWS. These characteristics vary in extent and intensity due to various factors including: the genetic type of PWS, background genetic and environmental variations between individuals with PWS, the level of support for the family, and early treatment, for example, with growth hormone or early intervention to support parent-child interactions.

3. **Environment and behavioural expression:** The behaviours of concern and mental ill health in people with PWS that make up the neuropsychiatric phenotype arise to varying degrees as a result of the presence of a biological vulnerability and in the context of past and present environmental factors. These environmental factors may influence both the onset and persistence of particular behaviours over time. Specific factors may impact the severity and frequency of particular behaviours (e.g. emotional outbursts) and/or impact on the consequence of that behaviour for the person with PWS (e.g. the absence of controls over the food environment results in life-threatening obesity).

Dimensions of well-being

4.1.0 Influences and determinants of personal well-being

4.1.1 The studies of people with PWS and of their families describe how having a child with PWS impacts the quality of life of the person with PWS and their family.

Factors specifically relevant to PWS, such as weight gain and behaviour issues, influence outcomes along with those common to the general population and individuals with intellectual disabilities (Cohen et al., 2010; Mazheri et al., 2013; Wilson et al., 2016).

Given the evidence regarding well-being and the quality of life of people with PWS, our approach is to start with the assumption that influences on quality of life and personal well-being in the typically developing population, as well as in populations of people with intellectual disabilities, are likely to be relevant for people with PWS. However, these must be understood within the unique context of PWS-specific characteristics and associated needs.

4.1.2 Surveys in the general population in the western world tend to show that people identify the following needs as important to their mental well-being:

1. physical and mental health
2. financial security and stable accommodation
3. social support and personal connections
4. a sense of independence (autonomy)
5. feelings of usefulness or purpose in life

In all of these components, 'adequate' is subjective and will vary between individuals, families, countries, and cultures. It is for this reason that some people report having a good quality of life and are contented, and while others with similar resources and opportunities may not be.

It is also important to recognise that the stated priorities will vary across countries and may be different from those listed here.

4.1.3 There are different concepts of quality of life. Much of the research on one of these concepts, the shared quality of life of people with intellectual disabilities, is based on characteristics of human life and human environments that are common to all people.

For example, the importance of social support from family, friends, and co-workers is usually highly valued. These shared characteristics of quality of life align with human rights, which recognise a set of fundamental rights and freedoms that belong to every person, from birth to death (see Bertelli & Brown, 2006).

4.1.4 As quality of life is very subjective, what is seen as positive for one person may not be in the case of another.

Personal differences within the PWS population can be substantial, as genetic makeup, individual personality, early life experiences, or environmental conditions vary, and each of these may shape the way quality of life is viewed by the individual.

There will be differences in the way a person experiences the impact of their particular impairments (disabilities) in terms of the nature of their functional abilities and the resulting subjective and objective consequences that result.

4.1.5 Additionally, all individuals have unique interests, which are sometimes very meaningful to their lives, enriching their life quality, but these interests may hold little meaning for another person – examples include a particular hobby, specific religious beliefs, or personal passions. Any consideration of well-being and quality of life must consider how these interests impact the individual.

4.1.6 Typical social determinants of quality of life include poverty, poor housing, unemployment, and social isolation. There is evidence that people with intellectual disabilities and their families face an increased risk of being exposed to these negative social determinants of poorer health, quality of life, and well-being (Kirkbride et al., 2024).

Higher rates of mental and physical health issues are common among people with intellectual disabilities and may be linked to the specific causes of their disabilities. For children and adults with PWS, this includes the risk of severe obesity and its complications, together with a spectrum of behaviours of concern and mental ill health.

A limited understanding of health risks in this population may result in delays in medical diagnoses and in accessing necessary services, further increasing the severity and impact on well-being (Feighan et al., 2019).

4.1.7 An example of how circumstances may have a very specific impact on health is seen in the findings from a study conducted in South Africa. In this study it was evident that socioeconomic circumstances contributed negatively in the families' attempts to manage the weight of individuals with PWS. The environmental modifications required to manage food-related problems were not possible because of inadequate housing space and financial constraints. The families only bought food they could afford and not the food suggested by the dietician (Sethuntsa, 2018).

4.1.8 Families report that caring for a person with PWS is exceptionally difficult, and studies have shown that caregivers have higher levels of stress (Mazaheri et al., 2013, Micallef Pulè & Hughes, 2025, Wong et al., 2020).

The impact of hyperphagia, anxiousness, and behavioural challenges seen in people with PWS have each been identified as especially stressful (Kayadjanian et al., 2021).

Caregiver stress can be both substantial and chronic, especially where caregivers are parents or family members.

Family caregivers typically experience diagnosis-related grief (Wayment & Brookshire, 2017), challenges of 'living with loss' (Mahmood et al., 2015), and stress that ranges from 'compassion fatigue' (Davenport & Zolnikov, 2021) to full-scale caregiver burnout (Jijon & Leonard, 2020). They frequently report feelings of guilt, isolation, uncertainty, and low self-esteem (Bravo-Benítez et al., 2019).

4.1.9 Parents who care for children with developmental disabilities have been found to exhibit increased rates of physical and mental ill health (Masefield et al., 2020), with their health deteriorating significantly as they get older, especially after they turn fifty (Namkung et al., 2018).

In a systematic review of nine studies that explore the impact of parental stress on their children with intellectually disabilities, high parental stress levels predicted subsequent emotional and behavioural problems in their school age children (Ribas et al., 2024).

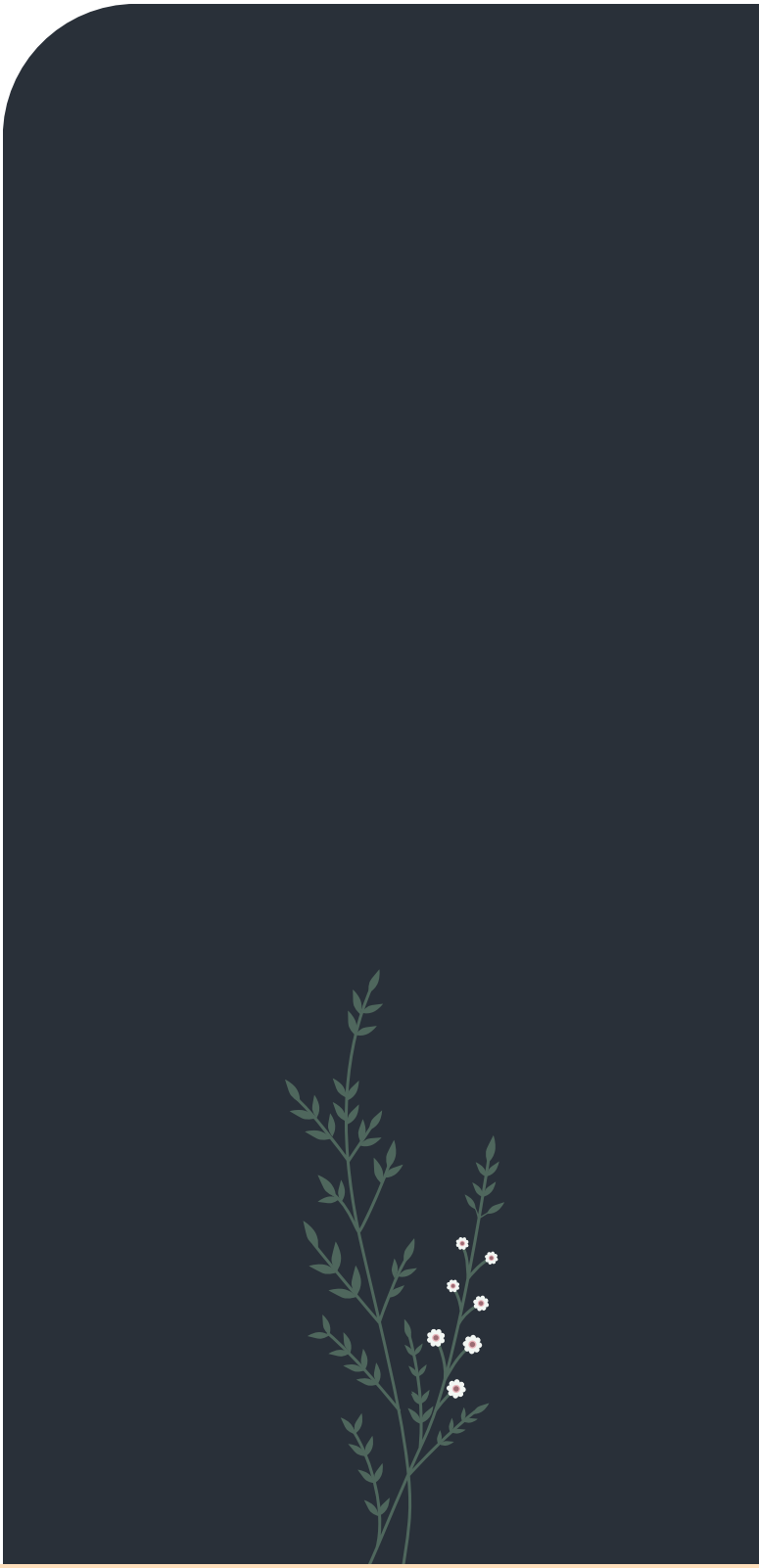
4.1.10 In a South African study caregivers were reported to dedicate most of their lives to taking care of their children with PWS. This caused disruptions to their own studies, job terminations, and the inability to secure full-time employment.

The primary caregivers found their sense of self-worth engulfed by the role of caring. They neglected their own needs because their main focus was taking care of and constantly monitoring their child with PWS.

The caring role has proven to be strenuous, time-consuming, overwhelming, and almost unbearable, and can lead to stress and struggles with coping. Some primary caregivers needed psychological support to help them manage their child's academic difficulties and behaviour problems both at home and at school.

The primary caregivers need external support to relieve them of their caregiving duties for a period of time and allow them time to focus on something other than the role of being a caregiver (Sethuntsa, 2018).

This study also revealed issues around stigma. This was evident in how 'others' accused primary caregivers of not disciplining their children, and how the primary caregivers also took responsibility and blame for their children's behaviour (Sethuntsa, 2018).



The harmful effects of caregiver stress are not confined to caregivers. Caregiver well-being directly affects the quality of life of individuals with PWS. Supporting caregivers is essential for positive outcomes. This is especially relevant in family caregiving, where collective resilience is greatly dependent on interconnected factors, such as effective communication and collaborative coping (Walsh, 2003). Stress reduces a carer's capacity to provide consistent support and feedback, and increases the risk of discord among family members.

Effective support for people with PWS relies heavily on effective management of the home environment, usually by family carers. In this respect, caregiver stress creates a vicious cycle. Because stress diminishes the quality and consistency of care that family members can provide, it further compromises the well-being of the person with PWS. As such, caregiver stress leads not only to poor outcomes for carers, it also undermines the well-being of those receiving care.

Occupational stress is also observed among direct support workers, particularly in relation to challenging behaviour and organisational factors. This can lead to high staff turnover and to inconsistences in support, which can impact adversely on the well-being of those being supported (see systematic review by Ryan et al., 2019). This is likely to be particularly relevant to people with PWS, who can find such change very difficult. On the other hand, it is important to acknowledge the very positive experiences of providing support as described by staff.

Promoting the well-being of a person with PWS will typically require consideration of the wider family/support context in which they live, and help in strengthening the capacity of the family and paid support staff to meet the significant challenges they face.

4.2.0 Choice, independence, and the material environment

4.2.1 As individuals with PWS grow older, they may, depending on the expectations and cultural norms where they live, gain more freedom to make their own choices and develop a sense of independence.

In many countries, this right to self-determination is legally protected, and is also clearly stated in the United Nations Convention on the Rights of Persons with Disabilities (UN CRPD).

However, for people with PWS, achieving this independence is a unique challenge. Impairments in higher order cognitive ability, including social cognition and executive functioning, may become evident and impact their wish and ability to lead an independent adult life (Holland et al., 2003).

4.2.2 Decisions a person with PWS makes may have adverse impacts on their physical and mental health, their social functioning, and on their quality of life.

Because of problems with satiety they may place excessive emphasis on food and its availability, with little regard for other quality of life factors such as having fun, enjoying music, attending school and being satisfied with their school performance or performance at work, and getting on well with parents or siblings.

They may also misinterpret social cues or find it difficult to recognise and accept that their present circumstances are problematic further impacting their quality of life by leading to conflicts with parents, classmates, or friends, which makes them worried and unhappy again (see Dykens et al., 2019).

In such situations trying to shift the focus onto a different task may cause anxiousness and be resisted (Woodcock et al., 2009).

4.2.3 In some cases, it may be unclear if a person with PWS's expressed views truly represent their feelings and desires, and there may be significant differences between how the person with PWS assesses their own quality of life compared to assessments made by their families or others (Wilson et al., 2016).

While similar discrepancies occur in families of children with other developmental disabilities (Swift et al., 2023), for people with PWS such conflicting views may be a manifestation of the impairments associated with the syndrome.

The following mechanisms may explain why a person with PWS may continue to report positive well-being and refuse to change their behaviour even when parents and caregivers believe that the subjective well-being of their child with PWS must be quite poor or that the views of the person with PWS are inconsistent. The primary informant about an individual's quality of life is usually considered to be the individual themselves (from around the age of 8), and only secondarily, the caregivers.

People with PWS often have an intense preoccupation with all matters concerning food, including when and where it will be available, and what food is to be expected. They may also have other non-food related preoccupations. These preoccupations prevent the person with PWS from balancing other considerations, including non-food related matters previously considered of importance to them, such as hobbies and activities.

People with PWS can keep fixedly to one course of action regardless of its consequences and its impact on their well-being. They may act impulsively and have great difficulty foreseeing the consequences of their actions, such as severe weight gain, and social challenges. This in turn may impact quality of life. This is because of rigidity of thinking, a tendency to perseveration, slow cognitive processing speed, and feelings of anxiousness that arise because of the cognitive demand required of them when changing from one course of action to another.

4.2.4 Studies have shown that having a child with PWS has a major impact on a family's financial stability.

In some countries financial support will be available. However, even with support, the time needed to provide adequate support often impacts the ability of family members to work.

A study in the USA reported that health-related costs were 8.8 times higher in those with PWS than in a comparison group (Shoffstall et al., 2016). A recent international study conducted by IPWSO indicated that worries over money and loss of income were a major concern for families, particularly in countries lacking robust financial support systems (Henry, 2021).

The financial circumstances of an individual with PWS and their family may be the main determinant of whether support is available because in some countries access to necessary support and expertise is contingent on the family having private funds.

4.2.5 Although financial stability is important for caregivers' quality of life, people with PWS generally do not express concerns about money. They may not worry about being able to access appropriate accommodation or having reasonable quality care. However, this is likely to be a major concern to parents.

Nonetheless, the funding availability will clearly impact the opportunities they have to make autonomous choices and, at the same time, avoid significant risks, such as the severe consequences of extreme obesity due to lack of support to manage the food environment.

4.2.6 In most cases, people with PWS may not have to worry about finding accommodation themselves. However, aspects of their accommodation, such as restrictions around food and interactions with fellow residents and authorities (parent or manager) may cause discontent.

Although there is no specific research on this issue, experience suggests that the presence of social support and contacts, having some degree of autonomy, and feeling useful, are significant determinants of well-being for people with PWS, just as they are in the general population.

Achieving these conditions may be particularly difficult for people with PWS because poor social cognition may impede social discourse and may make individuals with PWS reluctant to accept support.

4.2.7 The degree of impact these factors may have on quality of life depends on how well local services adapt their support to meet the needs of a person with PWS. For example, schools might need to provide a structured and more predictable learning environment and manage food access effectively.

Having informed support for the person with PWS and their family, and a social and cultural environment that works to include people with disabilities in society, including people with PWS, is essential.

The World Health Organization's (WHO) model of 'Impairments, Disabilities, and Handicaps' (WHO, 1980) and the more recent version, 'Functioning, Disability and Health' (WHO, 2001) provide useful frameworks for understanding how different components can impact well-being and mental health. This understanding can then guide effective interventions.

4.2.8 Based on the evidence and our knowledge of PWS, the main factors affecting well-being and quality of life for people with PWS are outlined below.

Factors specific particularly to having PWS that also have a major impact on well-being and quality of life are covered in the sections below.

People with PWS are at risk of social exclusion and their families are at risk of financial hardship, the latter also affecting parental quality of life. Alongside these challenges, other family-related social factors including the extent of the family network, or membership in community groups such as faith organisations or clubs, will impact the ability of the person with PWS to feel connected to a peer group enabling them to develop a sense of belonging and self-worth. Special adjustments by staff in school and community programmes, and access to both financial and practical support, can help reduce these risks.

In adult life the risk of social isolation is also considerable. This may stem from the person's own priorities, often centered around food, as well as from a lack of necessary supports or the absence of residential, employment, and recreational services adapted to meet their needs. People with PWS may wish to enjoy social activities with others who do not have PWS but the fact that the environment will not be 'food friendly' makes attendance problematic.

Individual risks impacting well-being include: the impact of hyperphagia on physical health and life expectancy, especially when not living in a food-secure environment, significant social and cognitive impairments which make friendships and engaging with others difficult, and the extent to which support services are available and the person with PWS is willing to engage.

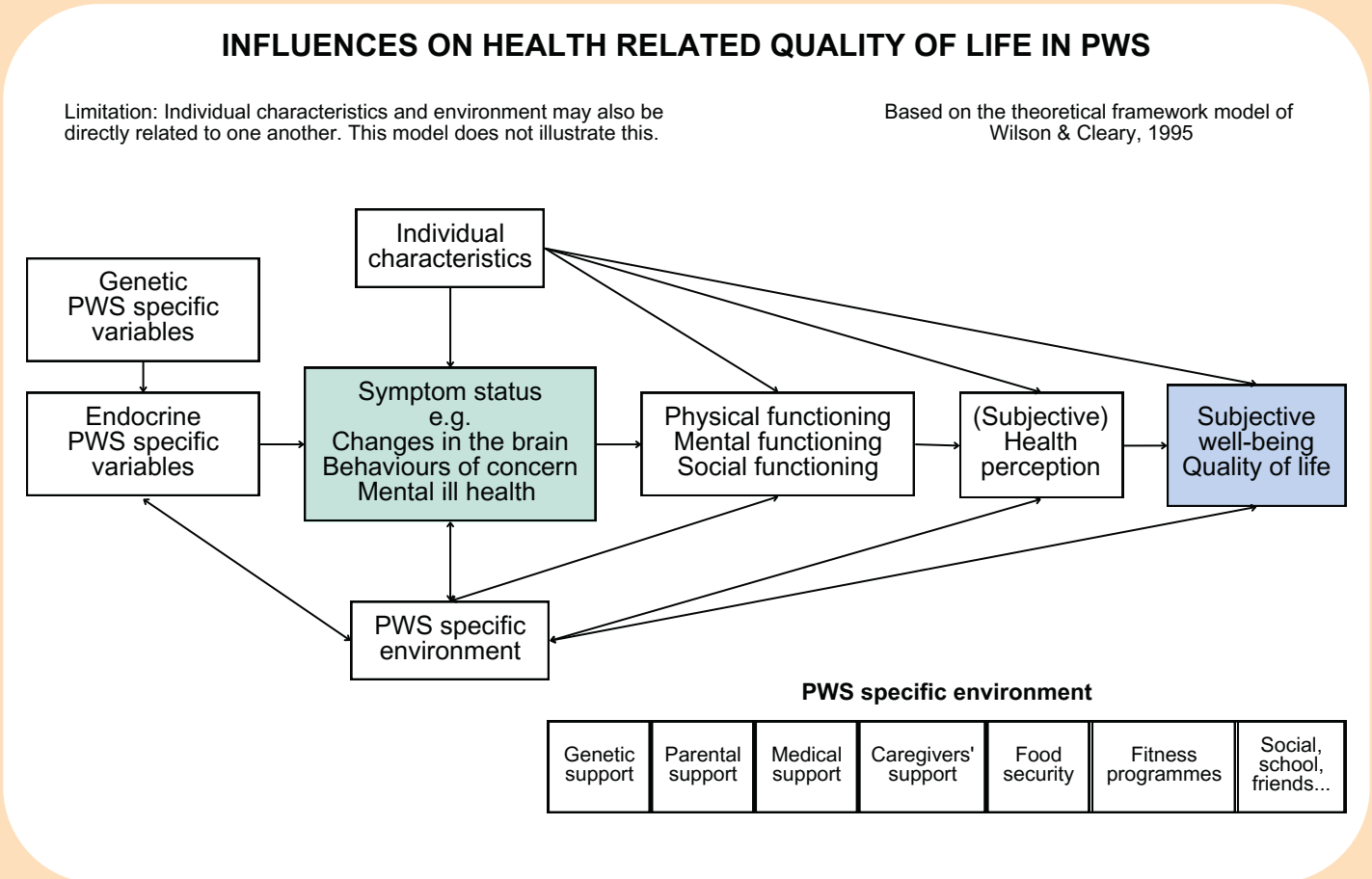


Figure 7 Diagram illustrating the model put forward by Wilson and Cleary 1995 and modified by Maria Huber to illustrate influences on Health Related Quality of Life for people with PWS. Courtesy of Maria Huber.

Dimensions of mental ill health in PWS

4.3.0 Interactions between biology and environment

4.3.1 As described in Part 3, many clinical studies have characterised what is known as the 'neuropsychiatric' and/or the 'cognitive and behavioural phenotype' of PWS.

We also refer in this Report to the different components of these phenotypes as dimensions of mental ill-health. These can be sub-divided into specific 'behaviours of concern' and particular abnormalities of mental state.

The term 'dimension' highlights that each exists on a continuum. Below we set out our understanding of the possible causal mechanisms that might explain the behavioural and neuropsychiatric phenotype of PWS, including hyperphagia, emotional outbursts, and self-harming behaviours as well as anxiousness, affective instability, and affective and psychotic illnesses.

4.3.2 The behavioural and mental health aspects of PWS are particularly complex to study, requiring a deep understanding of the brain and the impact of atypical brain development on cognition, behaviour, and mental state.

However, to fully comprehend why a particular behaviour, such as an emotional outburst, occurs at a given moment and persists over time, it is also essential to consider how factors in the environment can trigger and sustain these behaviours, and how wider systemic factors impact whether or not particular interventions can be implemented successfully.

4.3.3 The occurrence of behaviours of concern and mental ill health associated with PWS are best understood as the result of an interaction between atypical brain function, impaired cognition, and environmental circumstances.

Given the complex interplay between these three, we start this section by highlighting different relevant clinical perspectives that can provide a framework to aid understanding.

These frameworks can help organise thinking, deepen our understanding of the profile of mental ill health observed in individuals with PWS, including behaviours of concern, and provide the means to explain variations in severity and frequency of specific behaviours over time.

4.3.4 The models overlap, yet each offers unique strengths that can be valuable for specific situations, providing insights and guiding interventions.

Some behaviours or abnormal mental states may be predominately biologically-driven by the pathophysiology associated with PWS, while others might arise from physical or mental health issues or as a consequence of external events.

Additionally, some behaviours may be exacerbated by a dysfunctional and inconsistent care system, where underlying factors reinforcing the behaviour are not identified or addressed.

- **Developmental models** suggest that specific behaviours prevalent in those with particular neurodevelopmental syndromes such as PWS result from atypical or arrested development. These behaviours are part of the normal developmental trajectory but are expected to decrease or resolve as development progresses. This perspective is relevant to understanding the repetitive and ritualistic behaviours and the prevalence of emotional outbursts in PWS, which may be seen as a consequence of developmental delays that persist beyond typical developmental stages.

- **Biomedical models** focus on syndrome-specific deficits in brain function that directly influence behaviours or the onset of co-existing (co-morbid) mental disorders. These may be a consequence of the direct effects of the PWS genotype on brain function, or indirectly through its impact on brain development and the functioning of specific neural networks or neurotransmitter systems. Examples of behaviours linked to biomedical models include hyperphagia, affective disorders, and psychotic illness.

- **Neurocognitive models** link behaviours to the impact of atypical brain development affecting their cognitive and social abilities. For example, individuals with PWS may experience emotional outbursts due to cognitive overload resulting from an impaired ability to shift attention when unexpected change happens.

- **Psychological models**, particularly those based on learning theory, propose that behaviours are maintained, shaped, and reinforced by environmental contingencies. These models suggest that behaviours acquire a 'function', such as avoiding unpleasant demands, gaining attention, or obtaining rewards. Emotional outbursts and skin-picking, for example, may be reinforced over time by the responses they elicit from those in the environment around them.

- **Ecological (systemic) models** seek to understand human development and behaviour within a multi-level framework that includes the individual, the immediate family environment, and wider cultural and social contexts. These models also consider how transitions over time influence behaviour. An ecological perspective can therefore provide useful insights at times of transition or how variations in the environment can lead to a change in the frequency or severity of particular behaviours. This perspective can therefore be useful when designing interventions in shared living environments.

4.3.5 Together, these perspectives provide frameworks for exploring causal mechanisms that underpin different aspects of mental ill health at various levels, including the syndrome genotype, brain function, cognition, and environment. Woodcock and colleagues have developed such models based on their work comparing behaviour and cognitive profiles both within and between different neurodevelopmental syndromes. One such example taken from Woodcock et al., 2009 is shown in **Figure 8**.

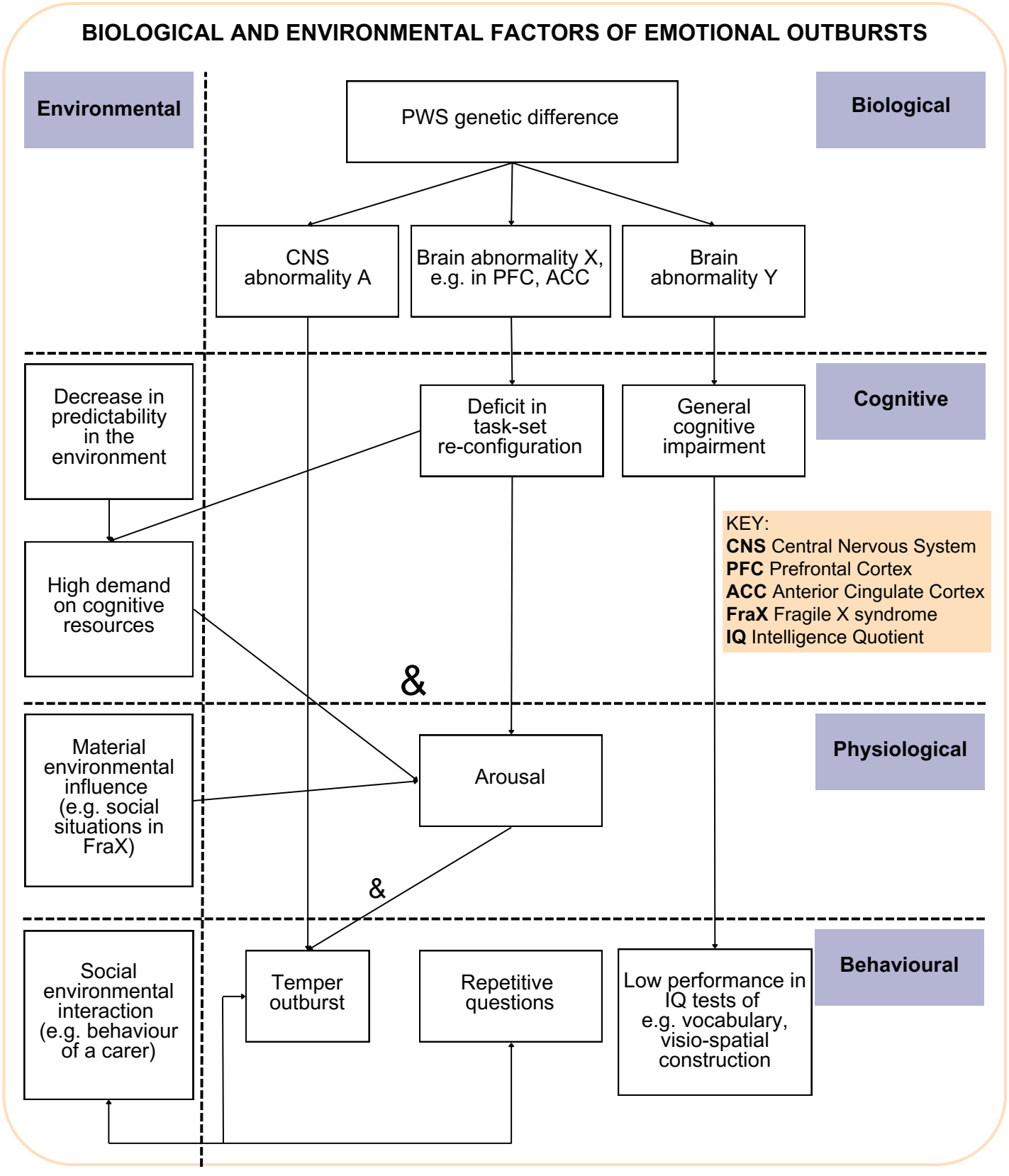


Figure 8 Figure adapted from Woodcock et al. (2009) to illustrate the different biological and environmental factors that underpin the risk of emotional outbursts.

4.3.6 Recent advances, particularly in neuroimaging, have led to new ways of conceptualising and investigating biomedical and neurocognitive impacts on psychopathology, one of the most prominent is the Research Domain Criteria (RDoC) framework (see Cuthbert, 2022).

Holland et al. (2019) and Salles et al. (2020) proposed that the above RDoC approach is highly applicable to the study of genetically-determined neurodevelopmental syndromes, such as PWS.

Using the RDoC approach, Thuilleux et al. (2017) conducted a detailed study of the psychopathological characteristics of 150 adults with PWS who had been hospitalised. Based on the RDoC criteria, they proposed a model for categorising individuals into groups based on cognitive, emotional, and behavioural features. Four distinct psychopathological profiles were defined: basic, impulsive, compulsive, and psychotic.

4.3.7 In the above study, the 'basic' profile was the most prevalent, found in 55% of the participants with PWS. The distribution for the other profiles was as follows: impulsive (19%), psychotic (19%), and compulsive (7%).

Notably, there were differences in the proportions of these profiles depending on whether the genetic type of PWS was a deletion or mUPD. In the deletion group 70% of individuals exhibited the basic profile, whereas in the mUPD group a higher percentage (43%) fell into the psychotic profile.

4.3.8 New approaches, such as that used by Thuilleux et al. (2017), offer a valuable perspective for understanding the underlying brain networks that are common to each RDoC category.

For example, neuroimaging studies have been used to investigate the brain areas and neural pathways involved in PWS with intra-regional and inter-regional deficits in functional connectivity (Huang et al., 2024) being identified.

Such methodologies are just beginning to be applied to our understanding of the PWS neuropsychiatric phenotype. In the following section, we will consider what is known about the potential causal mechanisms for behaviours of concern and mental ill health in PWS.

4.4.0 The PWS genotype and the neuropsychiatric phenotype

4.4.1 At the level of the genotype, a key question is whether direct or indirect causal links can be established between the absence of expression of specific maternally imprinted genes and the various dimensions of mental ill health commonly observed in people with PWS.

Clinical studies of people with PWS, those with small or atypical deletions on chromosome 15 (Duker et al., 2010, Sahoo et al., 2008), and the study of different genetically-modified mouse and other animal models of PWS have been the primary methods used to investigate genotype/phenotype associations (see Isles, 2022).

4.4.2 As summarised in Part 1, the gene SNORD116 on chromosome 15, which is paternally expressed and maternally imprinted, is likely linked to PWS.

However, the absence of expression of other paternally expressed/maternally imprinted genes at the 15q11-13 locus may also be important, including MAGEL2 and other snoRNAs.

Imprinted genes, such as those located at 15q11-13, may regulate nutrient transport to the foetus. Many are expressed in the brain and placenta, and some also influence the expression of multiple other genes (Falaleeva et al., 2015).

4.4.3 Gilmore et al. (2023) further explored this topic using engineered stem cell lines derived from cells with small paternal deletions involving SNORD116, which were further modified to produce neurons.

The authors noted that the targets for 30 copies of individual orphan SNORD116C/D box small nuclear RNAs were previously unknown.

Their study identified 42 dysregulated genes showing altered expression levels, originating from both within and outside the deleted region. The authors proposed that this combination of gene dysregulation most likely explains the PWS phenotype.

4.4.4 It is also clear that the PWS genotype significantly influences brain development, especially the hypothalamus and cortex (Manning et al., 2015).

Recent evidence, using advanced neuroimaging techniques, has shown that impaired brain development in people with PWS is associated with the presence of a small hypothalamus compared to both aged-matched typically developing controls, individuals with obesity unrelated to PWS, and people with anorexia nervosa (Brown et al., 2022).

4.4.5 Seeking to explain genotype/phenotype links one model proposes that some of the core aspects of the PWS phenotype (e.g. hyperphagia, skin-picking, affective disorder etc) can be traced back at a cellular level to the atypical pattern of gene expression resulting from the PWS genotype.

Examples include:

- **Necdin gene:** loss of necdin expression in mice has been associated with hypothalamic dysfunction, and increased skin-scraping activity, which serves as a model for skin-picking in PWS (Muscatelli et al., 2000).

- **Magel2 and SNORD116:** the absence of expression of these genes disrupts central regulatory pathways in the hypothalamus. This impairs the response to gut signals and the activation of satiety pathways, ultimately resulting in hyperphagia (Correa-da-Silva et al., 2021, Polex-Wolf et al., 2018, Rodriguez & Zigman., 2018).

4.4.6 An alternative perspective and second model is that the PWS phenotype arises primarily from the influence of the PWS genotype on brain development, which leads to alterations in the structure and function of the hypothalamus, as well as cortical and sub-cortical networks.

These disruptions contribute to the neuropsychiatric phenotype of PWS.

Examples include:

- **Cognitive and emotional impairments:** Atypical brain development results in specific cognitive deficits and difficulties with emotional regulation. As a result, emotional outbursts may occur under certain environmental conditions.

- **Homeostatic dysregulation:** Impaired brain development, particularly affecting the hypothalamus, leads to disrupted homeostatic regulation of emotions and an ineffective satiety response following food intake.

4.5.0 Atypical brain development in PWS: Explaining the neuropsychiatric phenotype

4.5.1 The characteristics of many aspects of the PWS phenotype support the notion of intrinsic dysfunction in neural and endocrine pathways (Tauber & Höybye, 2021).

This dysfunction results in homeostatic dysregulation and an imbalance between excitatory and inhibitory mechanisms in the brain, including the functioning of the autonomic nervous system.

Autonomic Nervous System (ANS) dysfunction, shown as an imbalance between sympathetic and parasympathetic tone, may contribute dynamically to behaviours characteristic of PWS (see **Figure 9**).

For instance, aspects of the PWS behavioural phenotype, such as a predisposition to emotional outbursts, may well be best understood as a consequence of an impaired autonomic coping mechanism.

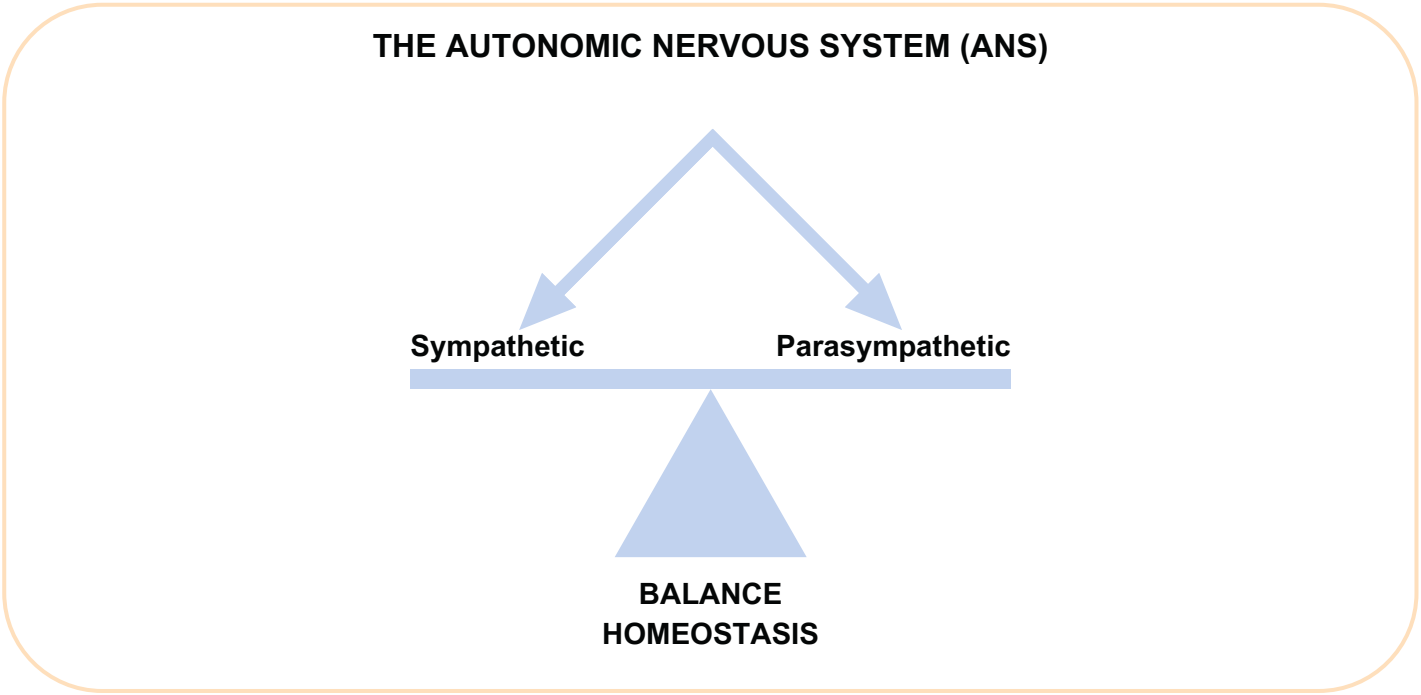


Figure 9 Diagram illustrating the balance between the two components of the autonomic nervous system, the parasympathetic (primarily the vagus nerve) and sympathetic. Courtesy of Janice Forster.

4.5.2 Brain development in PWS is further complicated by the impact of the early phenotype on later developmental stages. For instance, one proposed theory is that neonatal hypotonia impacts on the subsequent psychomotor development of the infant, particularly in terms of sensory motor experiences.

Another hypothesis suggests that the loss of expression of the imprinted gene Necdin results in increased apoptosis (cell death), impairing muscle differentiation, pruning, and bundling.

Additionally, loss of necdin expression impedes the maturation of neurons in the dorsal root spinal cord, impairing sensory coding and reducing awareness of pain and temperature sensations (Kuwajima, 2010).

4.5.3 It is proposed that sensory processing deficits are exacerbated by sensory gating abnormalities due to GABA receptor deficiency. As a result, insufficient stimuli reach the brain (Cromwell et al., 2008, Mendell, 2014).

Impaired sensory stimulation during the critical first year can, in theory, result in sensory deprivation (Cascio, 2010).

Consequently, it is argued that more intense sensory input might be needed to meet this heightened neurological threshold (Jovellar-Isiegas et al., 2020).

In addition, longitudinal studies suggest that sensory hunger-seeking behaviours are associated with impaired development of joint attention, social interaction, and nonverbal communication, and the emergence of repetitive behaviours (Baranek et al., 2018, Damiano-Goodwin et al., 2017, Foss-Feig et al., 2012, Watson et al., 2011). The extent to which this applies to PWS is uncertain.

4.5.4 We do not know the extent to which the above applies to PWS but is has been suggested that sensory hunger may predispose to the following:

- Stereotypic behaviours (skin-picking)
- Sensory seeking (foraging and collecting)
- Oral/ingestive (hyperphagia, rumination)
- Excessive and repetitive behaviours (habits)

Given that such hypotheses have not been empirically tested in people with PWS, it remains unknown whether or not additional sensory stimulation from early childhood would bring benefit or could pose risks for people with PWS. Some families support such a view but empirical research is needed.

4.5.5 There is also a question as to whether impaired reciprocal social interactions in childhood affects the subsequent development of theory of mind and social functioning later in life.

Lester (2019) highlighted the specific difficulties that infants with PWS have in recognising and processing visual social cues and in interpreting social situations (see also Dimitropoulos, Ho, & Feldman 2013).

Research also indicates that children with pervasive developmental disorders, who display significant deficits in emotional perception, subsequently experience more severe social impairments (Braverman, Fein, Lucci, & Waterhouse, 1989).

4.5.6 Research measuring the specific abilities required to interpret visual social information has shown that participants with PWS have significant difficulties organising visual information into coherent social narratives.

Participants were only able to correctly interpret 15% of the salient information provided (Koenig, Klin, & Schultz 2004).

Additionally, studies examining social and emotional processing in adolescents and adults with PWS have highlighted possible differences in their attention to, and recognition of, faces and emotional expressions.

Difficulties assessing facial expressions in PWS appear comparable to those observed in people with Autism Spectrum Disorders (Key, Jones, & Dykens, 2013, Rice et al., 2018).

4.5.7 The ability to process and respond correctly to facial emotional expressions is critical for an infant's interaction with those in their environment.

Impairments in emotional processing have also been linked to deficits in social functioning in adulthood (Philip et al., 2010).

Among emotional expressions, fear has been extensively researched due to its evolutionary role in protecting infants from harm. Studies indicate that typically developing infants show increasing attention to fearful expressions during the first year of life (Gartstein et al., 2010), with heightened sensitivity to negative emotions emerging between five and seven months of age (Peltola et al., 2009).

4.5.8 While there is little research on emotional expression processing in infants with PWS, studies on adults with PWS have revealed difficulties in emotional processing.

Whittington & Holland (2011) reported that in adults with PWS only 55% of facial emotions, including fear, were correctly identified, with fear being the least recognised, being identified correctly only 37% of the time.

Furthermore, those with PWS who had had a depressive illness exhibited selective impairments in fear recognition. This trait is associated with depressive illness in typically developing individuals, suggesting that this deficit may be an early marker of depressive illness in PWS.

4.5.9 Structural and functional neuroimaging studies provide further evidence of the extent of atypical brain development in individuals with PWS, revealing a range of impairments across various brain regions (Manning et al., 2019, Mantoulan et al., 2011).

Aberrant activity is observed across distributed neural networks, with those involved in controlling eating behaviour being the most extensively investigated.

Overall, abnormalities in brain structure and function are significant and can be summarised as follows:

- **Cortical and sub-cortical impairments:** Developmental delays in infancy and childhood are linked to impaired development of cortical and sub-cortical brain structures. These delays contribute to impaired intellectual, cognitive, and social development, leading to functional disabilities as described in Part 2.

- **Impact of early phenotypic features:** Early aspects of the PWS phenotype, such as hypotonia, are predicted to further exacerbate developmental challenges. These features may contribute to theories about what has been termed 'sensory hunger', increasing the risk for specific behaviours and worsening social impairments.

- **Hypothalamic Dysfunction:** Impaired development and functioning of the hypothalamus, along with its afferent and efferent connections, result in aberrant homeostatic regulation.

  This affects the following abilities:
  - The maintenance of energy balance relative to energy needs.
  - Growth and sexual development, impacting reproductive fitness in adulthood.
  - The regulation of temperature, mood, and behaviour via the hypothalamic pituitary axis and the autonomic nervous system in response to changes in physical and social environments.

4.5.10 As illustrated in **Figure 10**, atypical brain development in people with PWS and the functional consequences, as described earlier, create internal conditions that increase the likelihood of mental ill health, including behaviours of concern.

One hypothesis suggests that people with PWS have an incomplete and inaccurate representation of both their internal world (their bodily needs) and their external world (social understanding, threat perception, etc.).

These imprecise representations in the brain of internal and external worlds creates a feeling of uncertainty and shapes their responses, such as deciding whether to stop eating or whether to engage socially. The outputs of the decision-making are potentially based on faulty inputs and are more prone to error (Holland et al., 2022).

In the next section we consider further possible mechanisms that explain specific aspects of the neuropsychiatric and behavioural phenotype of PWS.

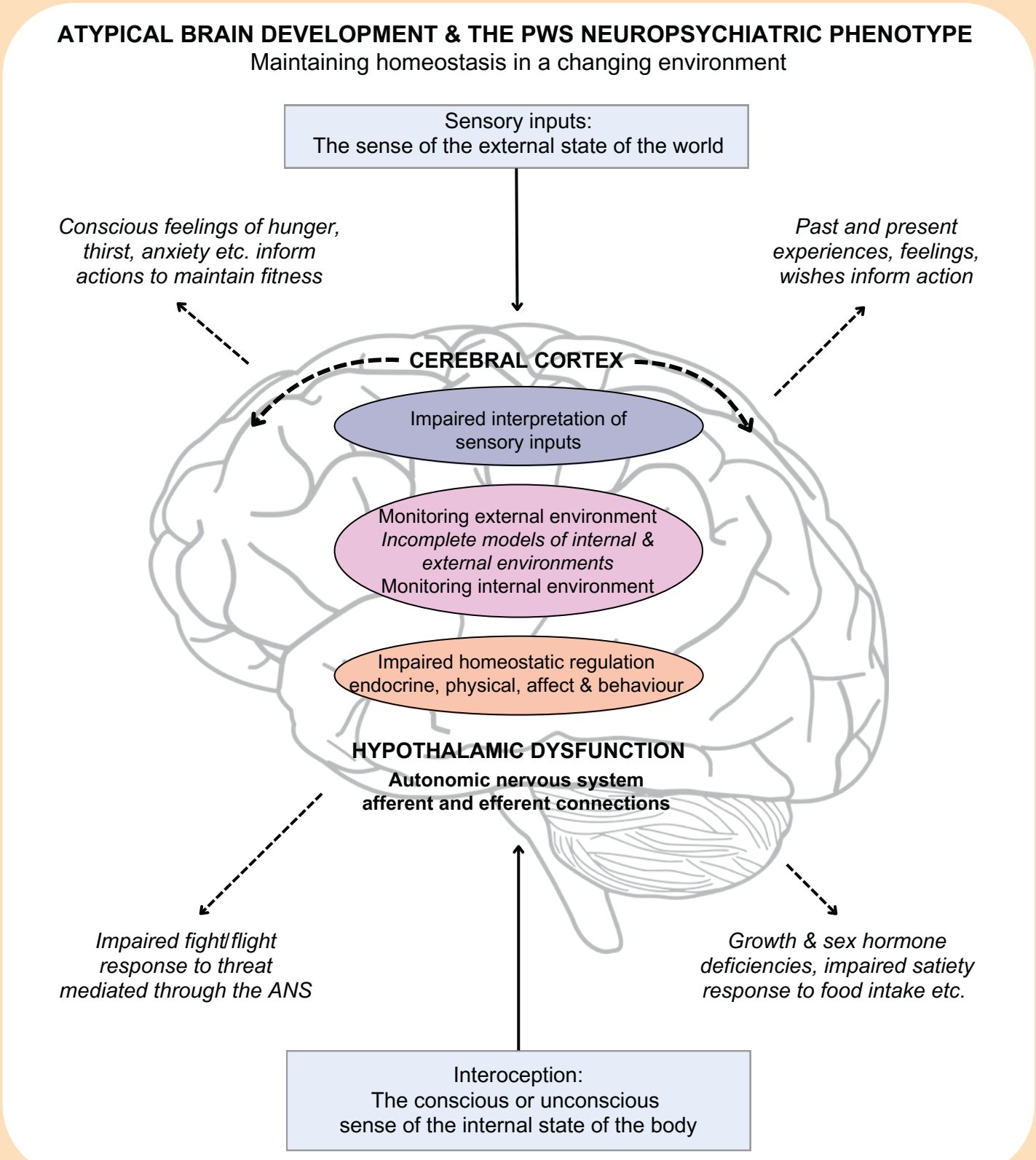


Figure 10 An illustration of the relationship between sensory and interoceptive inputs and the brain's role as a decision-making organ forming internal models of the environment and responding to need.

Toward a current understanding of causal mechanisms

4.6.0 Current understanding of mechanisms underlying hyperphagia

4.6.1 Transition from hypophagia in infancy and early childhood to hyperphagia in childhood is a central characteristic of PWS (see Part 1). However, the mechanisms underlying this shift from the initial hypophagia, together with failure to thrive, to hyperphagia and a heightened risk of severe obesity, remain unclear.

One explanatory model is that of Kinship Theory (Haig & Wharton, 2003; see Eggerman et al., 2021 for review). This theory suggests that gender of origin imprinted genes emerged in mammals due to different evolutionary pressures on male and female lineages.

In the case of PWS the maternally imprinted genes, whose absence of expression results in PWS, became imprinted because of their role in regulating energy (food) intake both in pregnancy and subsequently in infancy and childhood.

4.6.2 The work of Antonio and Hanna Damasio (2022) helps us understand the internal mental states of people with PWS and why their eating behaviour is dysregulated. They proposed that feelings of hunger and satiation are the conscious expressions of homeostatic processes that are responsible for the regulation of food intake.

Normally changes in these feelings trigger food-seeking behaviour and then, as food is consumed, lead to cessation of eating as fullness increases and the desire to eat decreases.

This finely tuned system relies on effectively functioning hypothalamic pathways and nuclei, as well as hormonal feedback from the gut via the blood and from afferent and efferent connections of the vagus nerve (see below). Together, these mechanisms ensure that food intake and energy needs are balanced and optimal for survival.

4.6.3 The evidence clearly indicates that the above feedback loops are dysfunctional in people with PWS. For example, several observational studies conducted in controlled settings have shown that people with PWS fail to limit their calorie intake in line with their energy needs when compared to a control group (see, for example, Lindgren et al., 2000).

In another study (Holland et al., 1993) where participants had ad-libitum access to food for one hour, ratings taken every 20 minutes of hunger, desire to eat, and fullness changed in the anticipated directions during eating. However, the participants with PWS needed to consume three times the number of calories of a typically developing comparison group for these shifts in cognitions to occur, measured using a visual analogue scale.

This is very much in line with the work of Damasio as described above. It was also noted that, in people with PWS, feelings of hunger and desire to eat increased again shortly after access to food was stopped and much sooner than observed in the comparison group (Holland et al., 1993).

These findings indicate that for biological reasons hyperphagia in PWS is likely to result from an impaired ability to achieve satiation and, therefore, there remains an ongoing drive to eat, even though calorie needs have been exceeded.

4.6.4 Neuroimaging studies have shown atypical cerebral responses to food intake, characterised by excessive activation of reward pathways and a lack of activation in brain regions associated with satiety, such as the medial prefrontal cortex (Hinton et al., 2006, Holsen et al., 2006; 2009, 2012, Zhang et al., 2015).

While interpretations of these studies may differ, a consistent finding is that activation of cortical pathways responsible for interoceptive awareness and the cessation of eating behaviour, are unresponsive to calorific intake. This insensitivity suggests that the presence of an excessively high calorie threshold is needed for the cessation of eating.

4.6.5 As the cerebral underpinnings of obesity are studied and better understood, a distinction has been drawn between two related and overlapping concepts: appetite and hunger.

The former is seen as the desire to eat and arises quickly and is moderated via neural reward circuits. The latter is the need for food for survival and comes on slowly and is moderated by neural satiety circuits (Gibbons et al., 2019).

Holland et al. (2003) had earlier argued that PWS might be best conceptualised as 'a genetic model of starvation' in which sensations of hunger remained permanently high with little fluctuation before and after meals.

However, in the discussions that took place in the IMHN, not everyone agreed that hunger is increased in PWS. It was argued that the change in eating behaviour in infancy and subsequently across development may result from a change in the drive to eat related to maturation of reward circuits in the brain.

4.6.6 The question remains: what is the underlying pathophysiology that drives the insensitivity to satiety observed in PWS?

In other conditions, for example, gene mutations have been identified that result in loss of function within specific hypothalamic pathways, leading to impaired regulation of food intake (Farooqi & O'Rahilly, 2017, Thaker, 2017).

Under normal conditions, the hypothalamus regulates appetite by balancing signals from orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) pathways.

Orexigenic signals are primarily driven by neurons that release neuropeptide Y (NPY), agouti-related peptide (AGRP), and gamma-aminobutyric acid (GABA)—collectively referred to here as "NAG" neurons.

These are balanced by anorexigenic signals from pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons.

Additionally, higher cortical centres influence this system by modulating eating-related thoughts and behaviours, helping to maintain energy balance.

4.6.7 The importance of abnormalities of the hypothalamus in PWS was first recognised with the observation of a reduction in the number of oxytocin-producing cells in the paraventricular nucleus of the hypothalamus (Swaab, 1997).

This, it has been argued, may contribute to hyperphagia. However, trials of intranasal oxytocin therapy as a treatment for hyperphagia, have thus far shown only limited beneficial results (Rice et al, 2018).

More recent evidence using advanced neuroimaging analytical techniques, which enable precise measurement of hypothalamic size, indicates that the hypothalamus and hypothalamic nuclei are smaller in young adults with PWS compared to both age-matched controls and individuals with other causes of obesity.

Additionally, the authors report an inverse relationship between hypothalamic volume and hyperphagia – the smaller the hypothalamus the greater the level of hyperphagia (Brown et al., 2022).

4.6.8 The small size of the hypothalamus reported in the above study was attributed by the authors to impaired developmental processes, which may also account for associated deficits in sex and growth hormones and other hypothalamic-related aspects of the phenotype.

Reduced volume of the hypothalamic nuclei would likely result in reduced receptor availability, potentially contributing to the observed insensitivity to hormones, such as leptin, whose effect would normally be to reduce food intake. This is illustrated in **Figure 11**.

In an effectively functioning hypothalamus a balance is maintained between activation of neuropeptide Y (NPY), agouti-related peptide (AGRP), and gamma-aminobutyric acid) (GABA) neurons, on the one hand, and, pro-opiomelanocortin/cocaine and amphetamine regulated transcript (POMC/CART) neurons and their projections, on the other hand. Activation of the NAG neurons increase hunger and food-seeking behaviours, whilst activation of POMC/CART neurons signal downstream neuronal pathways, resulting in cessation of eating. Such changes in behaviour are a consequence of activation of areas of the cerebral cortex and changes in food-related cognitions.

Peripheral signals activate specific pathways in the hypothalamus to regulate food intake to match energy needs with energy expenditure by achieving a balance between activation of orexigenic and anorexigenic hypothalamic pathways, moderated by hormonal signals in the blood and activity of the vagus nerve. Increases in the hormone ghrelin increases food seeking behaviour, and other peripheral hormones, such as leptin (produced by fat cells) and cholecystokinin (CCK), peptide YY (PYY) and GLP-1 which are gut hormones, decrease such behaviour.

One hypothesis to explain the hyperphagia characteristic of PWS is that the small size of the hypothalamus results in reduced leptin receptor availability, creating, effectively, a state of leptin resistance. This resistance to the moderating effects of leptin and of other peripheral hormones results in unchecked activation of NPY and AGRP neurons and as a result of reduced activation of the POMC/CART neurons in the hypothalamic feeding pathways. Hyperphagia also impacts body composition in people with PWS, leading to a vicious cycle of worsening insulin-leptin resistance and unchecked orexigenic effects.

What is uncertain is the extent to which hyperphagia in people with PWS is fully explained by a failure of normal hypothalamic development and the resultant imbalance in the activation patterns of specific hypothalamic pathways prior to, during, and after eating. In this model, these hypothalamus pathways are present but are functioning less efficiently. Alternatively, deficits in hypothalamic pathways and the resultant dysregulation of eating behaviour may be as a result of the impact of the PWS genotype. These different perspectives have implications for treatment development.

As discussed in Part 5, importantly, treatments for hyperphagia in PWS that have been or are to be evaluated are in general acting on different pathways. Whether one or another treatment is more effective may also inform our understanding on the pathophysiology that underpins hyperphagia. However, it is important to note that both perspectives reinforce the view that it is for biological reasons that people with PWS are unable to effectively moderate their energy balance and over-eat.

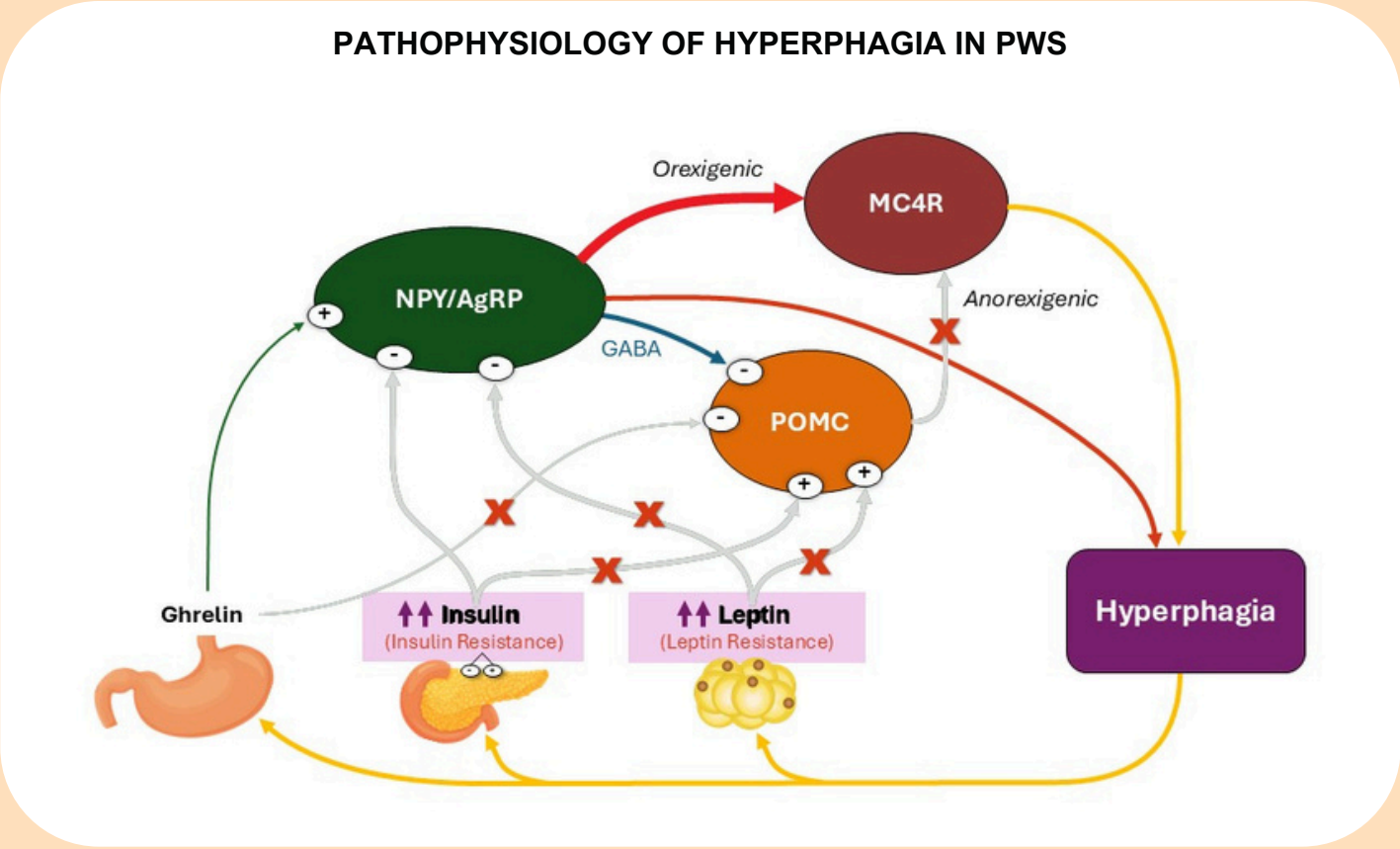


Figure 11 Diagram published in Wilkinson, Michael & Imran, S.. (2018). Neuroendocrine Regulation of Appetite and Body Weight. Courtesy of Deepan Singh.

4.7.0 Current understanding of mechanisms associated with other behaviours of concern

4.7.1 The behaviours associated with PWS, including emotional outbursts and skin-picking, we propose, result from an interaction between biological predispositions due to impaired brain development and environmental factors.

Earlier in this section, we described the impact of atypical brain development on cognitive and social functioning, as well as its impact on areas regulated by the hypothalamus, including central and peripheral neural connections and endocrine functions.

Research suggests that this atypical brain development specifically lowers the threshold for emotional outbursts in response to environmental stressors.

Contributing factors include:

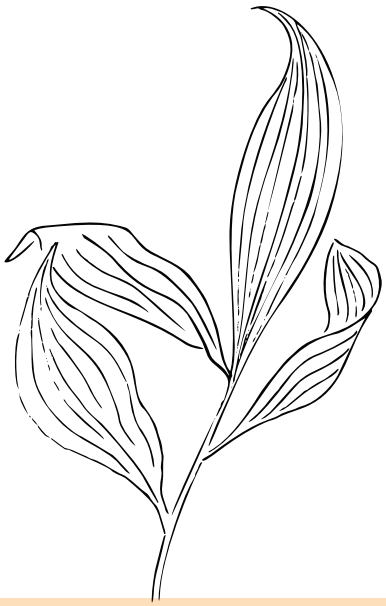
- **Cognitive impairments** that limit understanding of the social world for people with PWS, leading to misinterpretations of the actions and motives of others.
- **Cognitive inflexibility**, which reduces the ability to adapt to minor changes or life events, such as a change in routine and is associated with high levels of cognitive demand.
- **Impaired emotional regulation** results in a rapid escalation of emotional responses to an environmental challenge or disappointed expectations. This heightened emotional state further impairs coping mechanisms.
- **Altered perceptions of energy requirements**, due to the reduced ability of the hypothalamus and its extensive networks to respond to signals from the gut. Consequently, people with PWS may remain in a persistent emotional and cognitive state referred to as a 'hunting mode', characterised by heightened arousal and a focus on food-seeking behaviour.

4.7.2 In the following sections, we consider environmental influences on behaviour.

Behaviours such as emotional outbursts do not occur in isolation; they are often prompted by specific triggers and are less or more likely to occur under certain environmental circumstances (referred to as 'setting conditions').

Behaviours may serve a specific function, for example, to achieve expectations, to avoid demands, or to seek attention.

Identifying environmental contingencies surrounding behaviours can help identify why they occur, the circumstances under which they are likely to arise, and which environmental factors may be maintaining them over time.



4.7.3 An assessment process known as 'functional behaviour analysis' can help identify psychological mechanisms that may explain why behaviours occur under certain circumstances. By employing observational methods, this approach seeks to identify circumstances that predispose an individual to a particular behaviour, the triggers that initiate it, and what factors may sustain the behaviour over time. This is illustrated in **Figure 12**.

Additionally, behaviours may be automatically reinforcing, meaning they are inherently satisfying or rewarding without requiring external reinforcement. Examples of automatically reinforcing behaviours include eating, drinking, and scratching an itch.

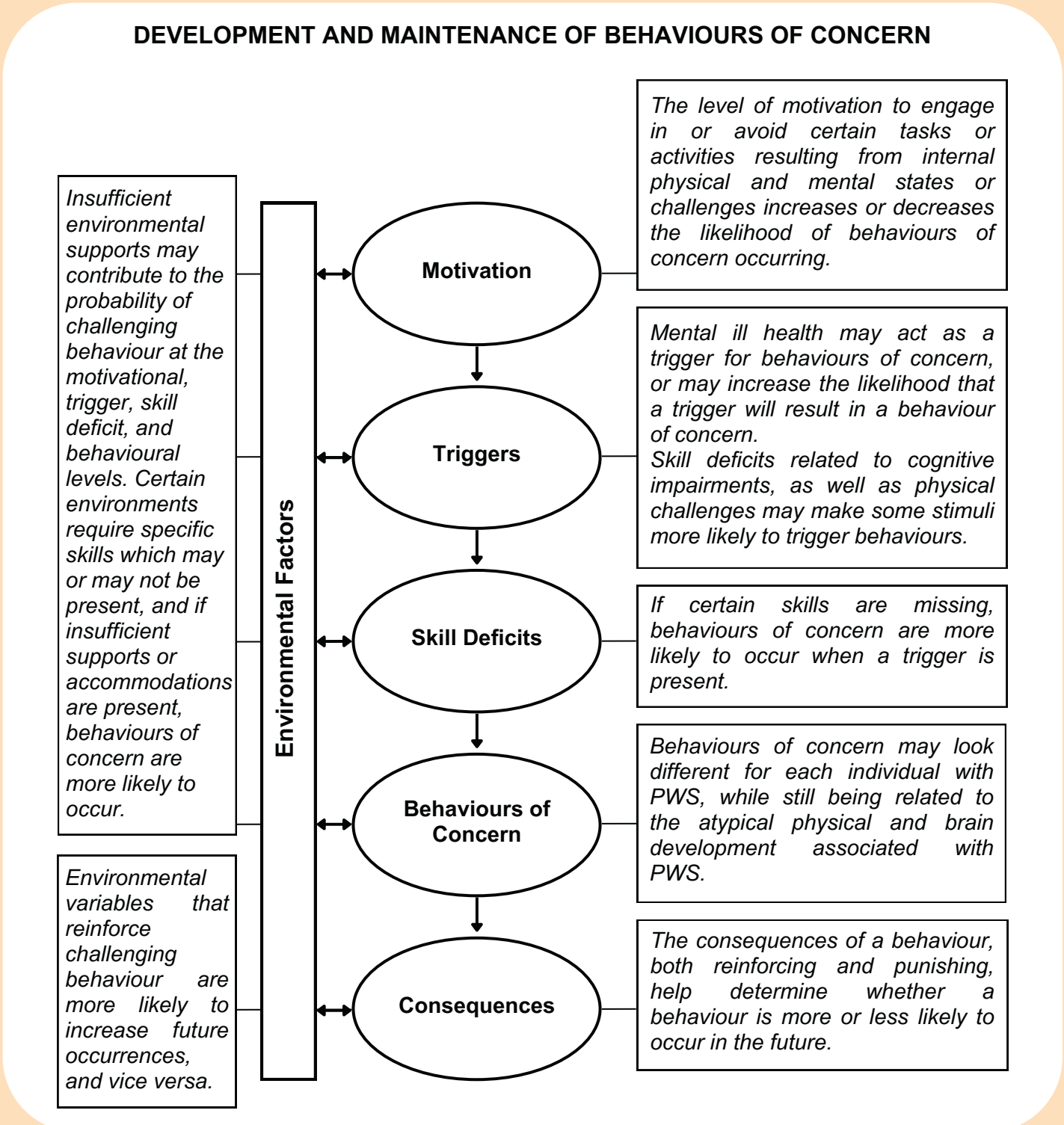


Figure 12 illustrates the assessment of behaviours of concern from a behavioural perspective. Courtesy of Kasey Bedard and Annette Griffith.

4.7.4 Due to atypical brain development, specific characteristic cognitive impairments associated with PWS act as risk factors for challenging behaviours, interacting with the environment and with factors that trigger and maintain the continuation of behaviours of concern.

For example, cognitive impairments lead to skill deficits that make it more challenging for people with PWS to navigate certain situations. An individual with PWS may have difficulty communicating their wants and needs, and this can escalate to challenging behaviour in an attempt to make their desires or requirements known.

Situations that require a high degree of impulse control, adaptability to changes in schedule, routine, or expectations, or the ability to transition quickly between tasks can be particularly challenging. These circumstances may trigger defiance and emotional outbursts (Tunnicliffe et al., 2013, Woodcock et al., 2011).

4.7.5 Because individuals with PWS struggle with emotional regulation and de-escalation, emotional outbursts can escalate quickly after a trigger and can last for extended periods.

The mechanisms behind emotional outbursts likely involve a combination of factors, including the high cognitive demand caused by environmental changes, impaired emotional regulation, and the presence of learned behaviours shaped by past experiences. The relative influence of these factors may vary depending on the specific situation.

4.7.6 Low mood or anxiousness may increase the likelihood of specific behaviours being triggered, impact a person's motivation to engage in adaptive behaviours, and contribute to increased irritability.

The onset of a psychotic illness or the presence of compulsive behaviour may lead to actions that are predominantly driven by internal states. However, environmental interventions to decrease stress can have a profound effect on anxiety and other internally driven states.

4.7.7 Similarly, physical impairments may also influence both the reinforcing and aversive aspects of a particular behaviour.

Challenges with fine and gross motor skills, along with daytime sleepiness, may make everyday tasks, such as self-care, work, and educational activities more difficult, and less rewarding. Over time these tasks may become aversive.

When people with PWS face unreasonable expectations, insufficient support, or limited access to desired items, they may escalate their behaviour to avoid these difficult tasks or to gain access to the desired items.

4.7.8 Once behaviours of concern emerge, they begin to interact with environmental factors, which can influence the likelihood that similar behaviours will occur again in the future.

Behaviours that are reinforced, such as gaining access to a desired item, receiving attention, or avoiding an undesirable but necessary task, are more likely to be repeated in the future. Conversely, behaviours that are not reinforced are less likely to recur.

It is especially difficult for a person with PWS to 'unlearn' an undesirable or habit behaviour. But, teaching new, adaptive, 'replacement behaviours' with reinforcement is a way to use their neurobiology for reward to improve daily function.

4.7.9 Environmental contingencies and behaviours of concern also interact with both mental well-being and mental ill health.

For example, uncontrolled food environments can heighten anxiousness, lead to food-seeking behaviours like stealing, and provoke emotional outbursts, ultimately harming both mental and physical well-being.

4.7.10 The underlying mechanisms contributing to body-focused self-harming behaviour (such as skin and rectal picking) in people with PWS remain uncertain, with evidence for both biological and environmental factors being important.

For example, abnormal grooming behaviour in mice genetically modified by knocking out the necdin gene potentially provides a model for understanding skin-picking in people with PWS (Muscatelli et al., 2000).

Necdin, a maternally-imprinted gene located at 15q11-13, has been linked to sensory neuronal development and an increased rate of apoptosis and heightened cell death in knockout mice has been observed (Andrieu et al., 2006).

4.7.11 Environmental settings lacking enrichment and social support may result in increased body-focused repetitive behaviours, as there are few external stimuli to compete with these behaviours (Hall et al., 2013, 2014).

These observations support the view that self-injurious behaviour arises in the context of a biological predisposition, which is more likely to manifest under specific environmental conditions.

However, an important question remains: why does this predisposition manifest as skin-picking rather than other forms of self-harm?

In addition to skin picking, rectal picking may occur, particularly in those with PWS due to mUPD, and inserting objects into body orifices is also described.

4.7.12 Although our understanding of body-focused self-harming behaviours in people with intellectual disabilities, and specifically those with PWS, is increasing, much remains hypothetical.

Notably, such behaviours often have particular characteristics (see Part 2) depending on the specific neurodevelopmental syndrome of the person affected, such as Lesch-Nyhan, Smith Magenis, or Fragile-X syndromes (see Symons, 2011 for review on self-injurious behaviour; also Oliver & Richards, 2015).

This pattern suggests the influence of a unique biological predisposition associated with each syndrome.

4.7.13 In PWS, the prevalent hypothesis is that skin-picking begins with the presence of a skin lesion or minor irritation, which triggers picking. This behaviour then causes a local inflammatory response, leading to more irritation and continued picking, creating a self-perpetuating cycle.

The concept of 'sensory hunger' suggests that individuals may engage in more intense picking to maximise the sensory input. Because of the high pain threshold in PWS, there is no significant pain to serve as a deterrent to this behaviour, so the cycle continues.

Interestingly, severe skin-picking behaviours have also been reported in children with congenital insensitivity to pain, highlighting a potential link between reduced pain perception and this form of self-injury.

Behaviours of concern emerge from the interplay of neurobiological impairments, cognitive deficits, and physiological responses, shaped by changing environmental demands.

Informed by these biopsychosocial interactive mechanistic models, clinicians must use history-taking, observations, and when necessary, further investigation and observation to identify the primary drivers for behaviours of concern in the individual with PWS, tailoring interventions accordingly (see Part 5).

Behavioural perspectives based on learning theory provide a theoretical framework for conducting analysis using information obtained from different sources and longitudinal observations.

4.8.0 Anxiety (or anxiousness), affective disorder, and psychotic illness: Investigating possible causation

4.8.1 In addition to the specific behaviours of concern discussed, Part 3 also addressed disturbances in affect and mental state, including anxiety, mood instability, bipolar disorder, and affective psychotic illnesses.

Traditionally, a distinction has been drawn between disorders of behaviour and disorders of mental state. The former have typically been viewed through the lens of psychological models of behaviour, such as learning theory, while the latter have been approached from a neuropsychiatric and brain-based perspective.

While this distinction has historically been useful in the field of intellectual disabilities, we argue that it is becoming increasingly blurred, particularly in the case of PWS, as our understanding grows of how environmental factors, setting conditions, and biological vulnerabilities interact.

4.8.2 Clinical observations, outcomes from clinical trials, and studies using genetically modified animal models of PWS provide some clues to possible mechanisms underlying the high risk of mental state disturbances.

Although the current evidence is limited, it suggests several plausible causative factors. We propose four mechanisms that are relevant to our understanding of the above in people with PWS.

The first three involve either the absence or atypical expression of genes located at or close to the PWS critical region on chromosome 15. The fourth is a consequence of excessive gene expression related to having an mUPD or an imprinting centre defect.

These mechanisms are summarised below.

1.) Atypical brain development and cognitive impairment: Individuals with PWS exhibit a pattern of atypical brain development that impairs cognitive functioning, particularly in social cognition.

As described earlier they may have an incomplete understanding of their needs and of the environment and this impacts their ability to respond appropriately to daily challenges.

As a result, people with PWS may experience high levels of intermittent or chronic stress, particularly in circumstances involving uncertainty around food or daily routines.

This stress contributes to increased anxiety (anxiousness) and mood dysregulation.

2.) Genetic influences on brain regulatory pathways: The absence or atypical expression of particular maternally-imprinted genes at 15q11-13, as well as neighbouring genes, such as those involved in the serotonergic and GABA receptor pathways, significantly affects key regulatory brain pathways.

These genetic changes alter thresholds in brain pathways that regulate mood and mental state, thereby increasing the risk of extreme mood fluctuations or abnormalities of mental state.

3.) Hypothalamic dysfunction and stress regulation: The hypothalamus in individuals with PWS is small and dysfunctional, impairing mood and behavioural dysregulation in response to environmental demands. This is likely to be a consequence of dysfunction of hypothalamic-pituitary-adrenal pathways and the autonomic nervous system.

This is further exacerbated by people with PWS having an increased exposure to high levels of stress. Together, these factors negatively impact the regulation of mood and behaviour under stress.

4.) Psychosis and excess gene expression in mUPD: In cases of psychotic illness, which are more common in teenagers and young adults with mUPD compared to those with a deletion, a different model is proposed.

Here, the causative factor it is hypothesised is excessive expression of specific genes with the opposite imprint on chromosome 15, such as UEB3A.

This excess expression may lead to an increased risk of psychosis (see Aman et al., 2018 for review).

4.8.3 Building on the above hypotheses, we consider the possible underlying causative mechanisms for abnormalities of mental state in people with PWS, including anxiety (anxiousness), affective instability, affective disorders, and psychotic illness.

Our framework is based on an interactive model that emphasises the interplay between biological vulnerabilities and environmental conditions.

4.8.4 Certain stress-inducing environmental conditions are particularly relevant for people with PWS, especially uncertainties around food. Managing these uncertainties, which we discuss in detail in Part 5, is a key area for targeted intervention.

We propose that the relative importance of biological pathways becomes increasingly significant when progressing from anxiousness, to affective disorders, and finally to psychotic illness.

Understanding these models is critical for developing effective interventions, which we address further in Part 5. Below, we consider each condition in detail.

4.8.5 Anxiety is often seen in people with PWS and is usually situational. For example, unexpected changes, such as delays in transportation, can trigger agitation, repetitive questioning, and general distress, sometimes culminating in an emotional outburst.

These episodes are often accompanied by repetitive questioning – ‘Why this?’ or ‘Why that?’. This repetitive questioning may be part of an adaptive response to the onset of an aversive event. The individual with PWS tries to process the sensory inputs and respond to make the environment more predictable (Woodcock et al., 2009).

4.8.6 The clinical presentation of anxiousness does not align with the characteristics of generalised anxiety disorder. Instead, it may be better understood as a psychological response to uncertainty.

As described earlier, people with PWS often have an incomplete internal representation of the world, making it harder for them to interpret and adapt to changing physical and social environments, and also to contextualise these changes over time. This heightened uncertainty can create a pervasive sense of threat.

As will be discussed in Part 5, effective interventions are therefore more likely to focus on psychological and environmental strategies, rather than relying on pharmacological approaches.

4.8.7 Several observations provide clues as to why people with PWS are at risk for affective instability, and why some may develop affective disorders or a bipolar-like clinical presentation.

Notably, those with PWS due to mUPD have a much higher risk of developing a psychotic illness than those with PWS due to a deletion (Aman et al., 2024, Boer et al., 2002).

This suggests that it is the unique genetic profile common to those with PWS due to mUPD, rather than the genetics shared across all forms of PWS, that is specifically linked to the development of psychosis.

4.8.8 Given these and similar clinical observations, a 'two-hit' model has been proposed.

In this model, having PWS (regardless of genetic type) constitutes the first 'hit', creating an increased baseline risk for affective instability and affective disorders.

The second 'hit', specific to individuals with PWS due to having an mUPD, further increases the risk for psychosis (Soni et al., 2007, 2008).

This raises a key question: what aspects of PWS, irrespective of genetic subtype, contribute to the heightened risk for affective disorders?

4.8.9 The hypothalamic-pituitary axis (HPA) is central to the body's homeostatic response to environmental changes and stress. Stress, in this context, is defined as the individual's way of coping with social and non-social stimuli that challenge or threaten survival, health, and reproductive success (see chapter by Rein et al., 2019).

The HPA axis comprises central neuropeptide components and peripheral endocrine organs. Corticotrophin-releasing hormone (CRH), produced in the paraventricular nucleus (PVN) of the hypothalamus, regulates both basal and stress-induced release of adrenocorticotrophic (ACTH).

CRH is also involved in other aspects of the stress response, such as arousal and autonomic activity. The PVN receives extensive input from various brain regions, including excitatory signals from the amygdala, and inhibitory signals from the hippocampus, as well as other parts of the limbic system and prefrontal cortex.

4.8.10 Glucocorticoids, such as cortisol and corticosterone, exert widespread effects on the brain and other organs. To prevent harmful effects from prolonged stress, the HPA axis employs feedback loops that shut down the stress response once the perceived threat has passed (this is reviewed in detail in Rein et al., 2019).

Although this physiological stress response is important and adaptive, prolonged or excessive exposure to stress may lead to illness, particularly depression, and also psychoses in vulnerable individuals.

4.8.11 There are two main reasons why the HPA axis may become maladaptive in people with PWS.

First, as noted earlier, people with PWS often experience high levels of stress because of impairments in sensory inputs from both their internal and external environments. These impairments lead to an abnormally incomplete internal model of the world, creating a heightened state of uncertainty.

Secondly, the impaired development of the hypothalamus compromises the body's ability to activate an effective response to stress. This function can best be understood as an impaired homeostatic response to social and environmental changes.

The combination of heightened uncertainty and stress, alongside hypothalamic impairments of developmental origin, results in a diminished capacity to regulate affective states effectively.

4.8.12 Studies comparing neural function in individuals with PWS due to deletions and those with mUPD have sought to identify underlying mechanisms that may explain the high risk of psychosis in mUPD (see Aman et al., 2018 for review).

At a genetic level, in large genome-wide association studies (GWAS), DNA copy number variants (CNVs) identified at or near the 15q11-13 PWS chromosomal region have been linked to developmental delay, autism spectrum conditions, and schizophrenia. (Isles et al., 2016).

This supports the hypothesis that when present in an individual, such DNA variants at that chromosomal locus confer an increased risk for having one or more of the above conditions due to an atypical pattern of gene expression of particular genes at that locus.

4.8.13 From a neurophysiological perspective, a study measuring event-related brain activity (ERPs) during a Go/No-Go task (Stauder et al., 2005) found reduced sensory processing speed in people with mUPD compared to those with deletion PWS.

Specifically, people with mUPD were reported to have significantly longer reaction times compared to those with deletion PWS and healthy controls. These delays were associated with deficits in both the N200 and P300 peaks, which are related to early modality-specific inhibition and late general inhibition, respectively.

In contrast, those with deletion PWS showed impairment only for N200 modulation.

4.8.14 Another study found that individuals with PWS exhibited a specific deficit in segregating human voices from a noisy background, and a failure to fully process sensory information before initiating a behavioural response. These deficits were again greater in those with mUPD compared to those with deletion PWS (Salles et al., 2016).

4.8.15 A study in children with PWS found significantly reduced white matter microstructure in most of the major white matter tracts in individuals with the mUPD subtype compared to those with deletion PWS.

These findings are similar to patterns that are observed in people with schizophrenia or those at ultra-high risk for psychosis (Lukoshe et al., 2017). These latter two populations have also demonstrated impaired processing speed (Karbasforoushan et al., 2015, Stauder et al., 2005, Whittington et al., 2004).

Additionally, Freedman et al., (2020) observed compromised P50 sensory gating in patients with schizophrenia as well as some of their unaffected relatives, suggesting a role for such impairments in the etiology of psychosis.

Similarly, impairments in both auditory processing and processing speed have been found in people with schizophrenia, those at risk for psychosis, and people with PWS due to mUPD.

These findings suggest common brain mechanisms among these groups, and highlight potential targets for treatment development.

Our knowledge of why people with PWS are prone to certain behaviours and abnormalities of mental state has improved significantly, though it remains incomplete. While having PWS must bring with it an increased risk for the onset of such problems during life, we argue that circumstances in the environment may also be critical. As yet, we have very limited understanding of how factors in early childhood may impact subsequent mental health later in life.

For people with PWS, their families, and for others who support them the task is to use the above knowledge and apply it to an understanding of an individual with PWS at that specific time and living within a particular physical and social environment. As will be considered in Part 5, it is this understanding that leads to informed interventions.

As understanding develops it will become clearer what aspects of the PWS neuropsychiatric phenotype are predominately, but not exclusively, a consequence of a single mechanism and/or which behaviours or abnormal mental states are more multifactorial in their aetiology. For example, hyperphagia may fundamentally be driven by abnormal brain biology and, in the absence of any specific treatment, the main approach is to prevent the consequences of hyperphagia through calorie restriction, controlled food access, psychological food security, and daily exercise. In contrast, emotional outbursts or skin picking may have several and varied factors that are aetiologically important.

In Part 5 we consider assessment and intervention. The development of interventions that are likely to be effective requires both an understanding of PWS and an understanding of the individual with PWS within the family and wider physical and social context.

Part 5: Shared best practices in the promotion of well-being and quality of life, and the assessment, prevention, and treatment of behaviours of concern and mental ill health in people with PWS

Introduction

5.0.0 Shared best practices in PWS mental health

5.0.1 In Part 2 of the Report, we defined well-being, quality of life, and mental health. While these concepts differ conceptually, each of them overlaps in that they are defined as being more than merely 'the absence of ill health', and their definitions include the presence of positive characteristics.

In Part 3, we focused on describing the specific dimensions of mental ill health, including the behaviours of concern and abnormalities of mental state that commonly affect people with PWS.

Part 4 examined the underlying mechanisms that may explain the occurrence of these behaviours and mental health challenges.

In this Part 5, we consider different types of interventions that aim to optimise quality of life and may be used to prevent and treat the PWS-specific dimensions of mental ill health.

As discussed, interventions can take place at various levels, including society, the family, and the person with PWS.

The three areas we consider are summarised below:

1. **Societal attitudes, family support, and the promotion of social inclusion:** Interventions undertaken at the societal level to provide an environment where children with specific neurodevelopmental conditions, such as PWS, and their families can be supported to thrive.

2. **Early intervention:** Efforts in early childhood that aim to optimise functioning, foster the development of communication and social skills, and provide education and support for parents.

3. **Targeted treatment approaches for the different aspects of PWS neuropsychiatric phenotype:** Interventions that aim to reduce the frequency and severity of mental ill health and behaviours of concern, while also equipping the person with PWS and their caregivers with the skills to effectively manage challenges when they arise.

5.0.2 We have chosen the term 'shared best practices' in the title of this part rather than simply 'best practice' for the following reasons:

- **Collaboration is essential:** Promoting well-being, and the prevention and treatment of the various dimensions of mental ill health associated with PWS invariably requires partnerships. Interventions are rarely passive (e.g. administering a medication); more often they involve active changes, for example, in support practices, new management approaches, or other strategies. For these to be effective it requires a shared understanding by those involved.
- **Context matters:** Shared practices should represent the best possible approach given the circumstances. What is feasible depends on several factors, including the emotional, practical, and financial resources of the family; the willingness of the person with PWS to accept the proposed interventions; access to adequate support and guidance; and broader cultural factors, such as societal views on disability.

5.0.3 Between countries, the structure of services and the availability of expertise vary markedly. However, as a general principle, the complex nature of early atypical development and the impact on the family of having a child with PWS means that responsibility for providing help to children and adults with PWS and their families extends beyond health professionals and associated health services.

Support for children and adults with PWS, and their families, must also involve government agencies at national and local levels, the private sector, civil society, non-governmental organisations (e.g. National PWS Associations). Education and social care services are also essential.

In specific cases, particularly in adult life, the criminal justice system may be involved. This can happen if a person's behaviour leads to interactions with law enforcement agencies.

5.0.4 The experience from the Mental Health Network is that when agencies do effectively work together, people with PWS can benefit and their families feel supported and know who to turn to when needing help. However, it is also clear that where agencies need to collaborate but fail to do so effectively, the consequences can be severe and at times tragic.

To create the conditions in which people with PWS have the best opportunity to develop and enjoy a good quality of life, two key elements are essential:

- first, a societal infrastructure that supports the realisation of the aspirations set out in the UN Convention on the Rights of Persons with Disabilities (UN CRPD);

- second, access to services that provide expert support and guidance for individuals with neurodevelopmental conditions such as PWS.

5.0.5 Even in countries with well-resourced health care systems, families often report serious gaps.

Services with the expertise to meet the behavioural and mental health needs of people with PWS are often unavailable. In other cases, staff in existing mental health or intellectual disability services lack the necessary knowledge or skills.

Some services have also imposed arbitrary barriers. As a result, people with PWS are denied the support they need.

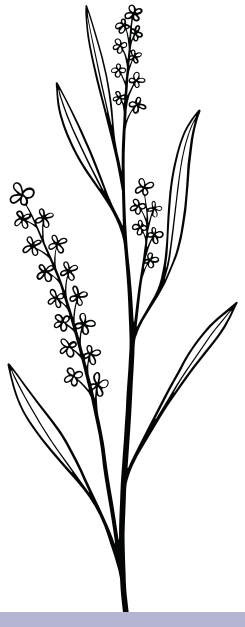
This is illustrated in the following case example.

A mother and her four children, including 10-year-old John who had PWS, had recently moved following her divorce. John had a history of severe emotional outbursts and had engaged in dangerous behaviour, such as trying to exit a moving car.

When their General Practitioner referred John to local services for help, his family was told that his disability was not severe enough to qualify for intellectual (learning) disability services. At the same time, the Child and Adolescent Mental Health Services were reluctant to accept him, as staff felt unprepared to support someone with PWS.

No policy was in place to ensure that individuals falling between service boundaries could still access the help they needed.

We consider what good services might look like at the end of this part of the Report.



Developmental context

5.1.0 Promoting and maintaining well-being, quality of life, and mental health

5.1.1 Based on the research specific to PWS (see Cohen et al., 2010, Mazaheri et al., 2013, Meade et al., 2021, Rozensztrauch & Śmigiel, 2022, Wilson et al., 2016) and the experience of clinicians and parents, we concluded in Part 4 that the factors contributing to and negatively impacting quality of life for the general population and individuals with other neurodevelopmental conditions are likely to equally apply to those with PWS.

In addition, there would be particular factors that are more specific to having PWS. Therefore to optimise well-being and quality of life for people with neurodevelopmental conditions, such as PWS, and that of their families, policies, practices, and services need to be in place which address those systemic factors that negatively impact on quality of life, including those more related to having PWS.

5.1.2 The extent to which this is possible and how it is undertaken will vary enormously across the world. It often depends on a country's financial resources, the availability of services and expertise, and the strength of civil society. Societal attitudes also matter, particularly those that support inclusion and challenge negative stereotypes.

Studies from the USA and other high-resource countries have identified key factors that influence quality of life (see, for example, Schalock et al., 2002). Most of these factors fall outside the scope of health services. Their relevance and priority may vary across cultures.

- Maintaining good physical and mental health
- Ensuring financial security
- The provision of acceptable living accommodation
- The promotion of social inclusion, including having a social network and personal contacts
- Enabling a sense of autonomy and a sense of contributing to society

5.1.3 While the above is true for children and adults with different rare and usually genetically determined neurodevelopmental conditions, there are also important differences between these various conditions. Addressing these will require a more syndrome-specific approach.

For example, people with PWS have been shown to experience high rates of both physical and mental ill health, which, in the absence of informed health support, may go unnoticed and untreated.

In food-insecure situations, people with PWS risk life-threatening obesity due to hyperphagia. This increases anxiety, worsens physical health, reduces mobility, and shortens life expectancy.

Impairments in cognitive functions, such as difficulties with sequencing, planning, shifting attention, understanding time, and recognising emotions, become more significant as these abilities become increasingly important in adult life. These higher order cognitive impairments can in themselves negatively impact quality of life for people with PWS.

However, the effects of such impairments can be significantly mitigated with informed and tailored support.

We therefore argue that at societal and service levels, countries should aim to provide the following:

- **Access to financial benefits and support** is crucial for facilitating social engagement and reducing the risk of additional challenges that arise from social isolation and financial hardship.

- **Educational, social, and employment services** should be customised and able to cater to the unique needs of individuals with complex disabilities and specific neurodevelopmental syndromes like PWS.

- **Access to health expertise that focuses on preventative strategies** to minimise the risk and severity of mental and physical health issues, the early detection of behavioural and mental health concerns, and guidance on appropriate treatments tailored to the needs of individuals with PWS.

- **Specialised guidance for professional caregivers and parents** to help them to understand the impact of the syndrome, particularly the behaviour. Together with support to help family members develop the necessary communication skills, to be able to handle challenging behaviour and to recognise the importance of an appropriate diet and regular exercise.

- **Opportunities for people with PWS to better understand their own syndrome** and to support their development of self-control around their emotions and eating behaviour.

5.1.4 The WHO model on Functioning, Disability and Health (**Figure 13**) below illustrates the interconnections between biological impairments, their impact on activities (function) and, subsequently, on participation.

Environmental and personal factors play a significant role in shaping the nature and extent of these relationships. Central to enabling participation for individuals with impairments is the provision of effective support.

High-quality support mitigates the disadvantages associated with cognitive and functional impairments by addressing the gap between an individual's competencies and their ability to engage with the opportunities available.

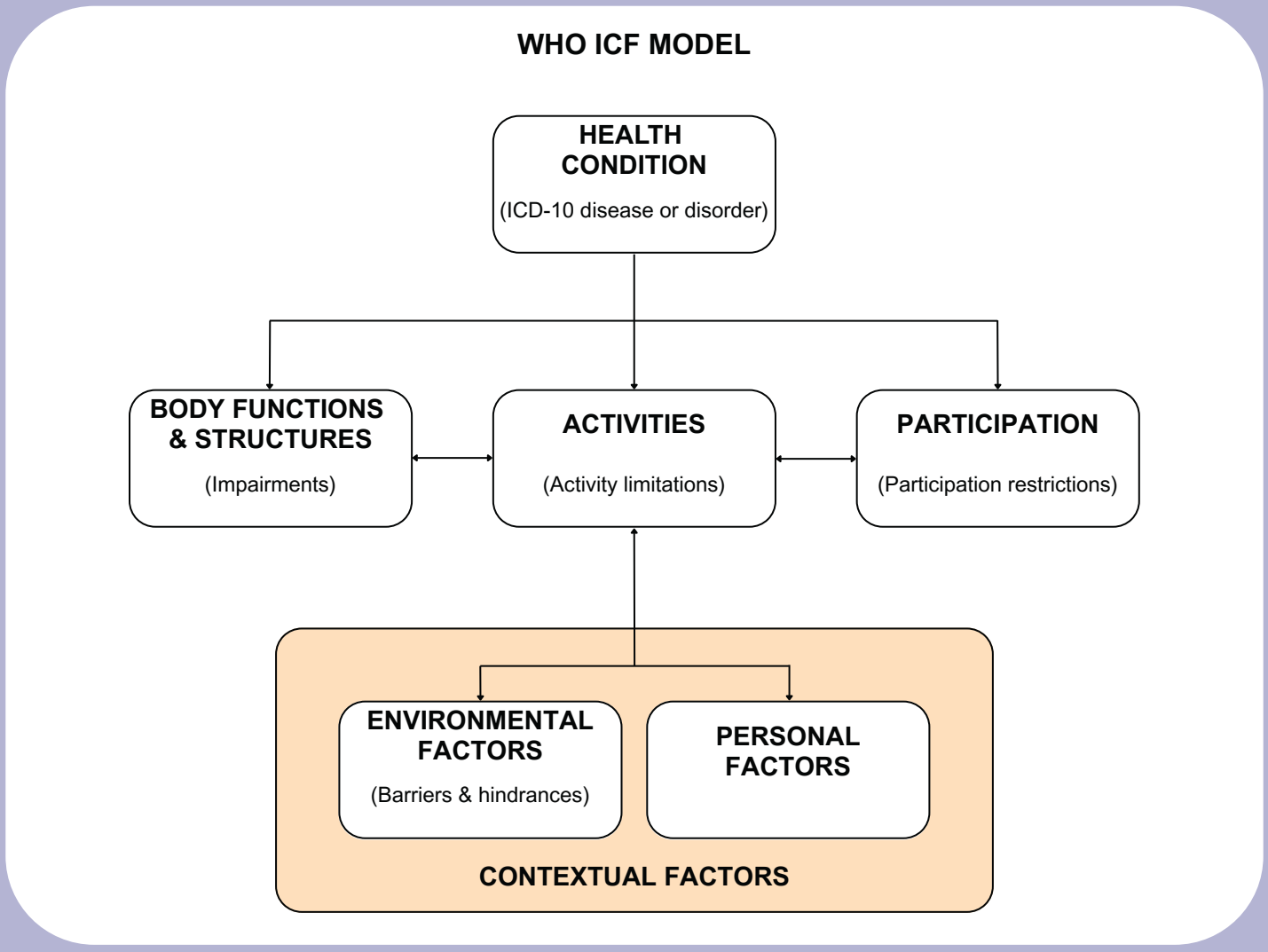


Figure 13 The World Health Organization's International Classification of Functioning, Disability and Health model of intellectual disability (WHO ICF model). Adapted from WHO (2011, p.18).

5.1.5 For people with PWS, unique challenges come with increasing age. This is largely about achieving the right balance between supporting teenagers and adults with PWS to make their own choices, on the one hand, and, on the other, limiting the harms that may result.

For example, restricting control over the finances of a person with PWS limits personal choice, yet for someone with PWS, this might be necessary to prevent excessive food purchases and reduce the risk of severe and potentially life-threatening obesity.

While the opportunities for financial independence increase with age, for adults with PWS, it is often necessary and important to carefully manage access to money. The approach to this should aim to maintain some autonomy and choice, while also mitigating the serious risks of excess purchasing of food.

Similarly, the ever-present risk of hyperphagia means that events, such as dining out and social occasions where food will be available, require careful planning to ensure safety and well-being (see sections below on managing hyperphagia).

5.1.6 When specialist residential services for people with PWS were first established, many of the residents who moved in were experiencing serious health issues due to extreme obesity. In response, strict physical controls around food access were put in place as a priority.

Now parents of young people with PWS are encouraged to help their child learn about PWS so that they can be involved in decisions about food, and better understand the risks of hyperphagia.

Some argue that this approach, which carefully allows for some independence around food, may enable the person with PWS to manage their eating, at least in part, and accept some of the restrictions if these are necessary. However, this strategy requires thoughtful and individualised consideration.

5.1.7 With increasing age, specific health needs may arise because of difficulties in the management of hyperphagia and the resultant development of severe obesity. These health needs include the risk of diabetes mellitus, obstructive sleep apnoea, and increasing physical limitations.

In the transition to adult life, the risk of obesity increases with greater freedoms, problematic behaviours may also increase when moving from the structure of formal education to the increasing demands and lack of structure that can follow.

This is also a time when serious mental ill health, such as a psychotic illness, may first develop. With transition into adult life, impairments in higher cognitive functioning become more apparent and these, in turn, may result in increases in challenging behaviour.

The resilience of a family may be repeatedly tested in this transition period, and it is under such circumstances that expert guidance and support, usually from health services, are required.

5.1.8 Teenagers with PWS may realise that they are different, will always have PWS, and will likely depend on others throughout their lifetime. They also may realise that they are unlikely to have children, may face social discrimination, and lack friends and peer support.

These feelings were all very apparent during the meeting with adults with PWS held at the conference in Ireland in 2022. Those with PWS participating expressed their concerns about social isolation, lack of meaningful activities, and very limited help with or opportunities for intimate relationships.

Some National PWS Associations have organised group support for their membership with PWS so that they are able to explore such feelings. Guidance on how to make meetings inclusive and supportive for people with PWS is available on the IPWSO website: www.ipwso.org/get-involved/guidance-on-pws-inclusive-meetings/.

5.1.6 As outlined throughout the Report, some needs of individuals with PWS overlap with those of others who have genetically determined neurodevelopmental syndromes, while others are unique to PWS.

Figure 14 outlines key 'best practice principles' specifically tailored to support people with PWS to maintain their well-being, quality of life, and good mental health. These principles are informed by published evidence of specific impairments in cognition and function associated with PWS because of atypical brain development (see Whittington & Holland, 2017 for review).

Each of these is explored in greater detail later in the Report. Importantly, these interventions can often be implemented at minimal financial cost.

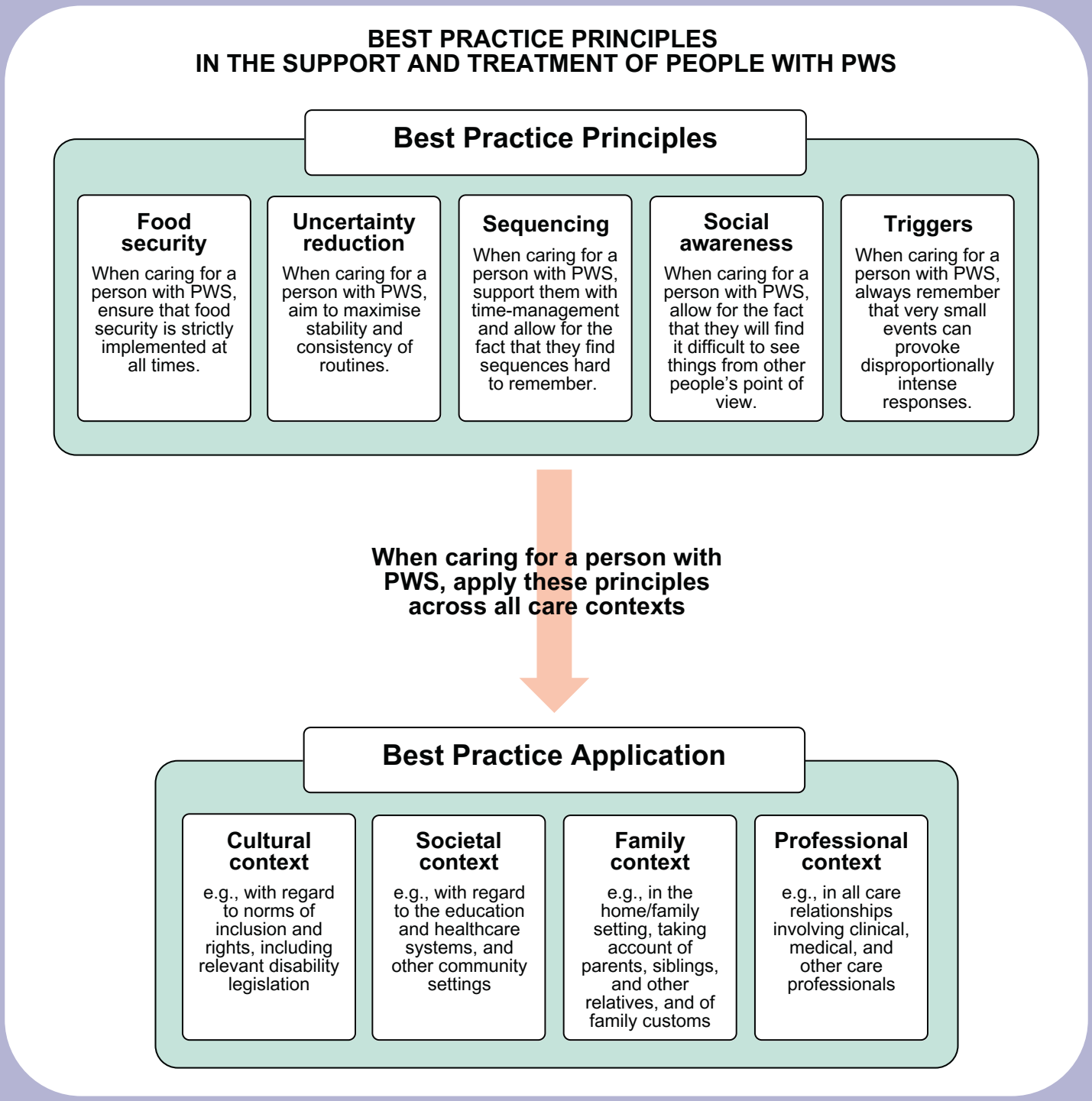


Figure 14 Diagram illustrating best practice principles in the support and treatment of people with PWS. Courtesy of Brian Hughes.

5.2.0 Importance of childhood

5.2.1 In Part 4 we discussed the psychological impact on parents of having a child with neurodevelopmental disabilities, including the experience of what have been referred to as 'diagnosis-related grief' and 'living with loss'.

This is inevitably a challenging time caring for a newborn baby who has significant complex health problems. Support and, when the parents feel able, access to knowledge about the condition affecting their child is crucial.

As our knowledge about PWS has advanced, the experience of many is that an early and accurate genetic diagnosis of PWS has the potential to transform the early lives of affected children. It also has the potential to help ensure positive physical and mental health and improved behavioural outcomes through providing anticipatory guidance.

When families have access to support and information from national PWS Associations, IPWSO, or paediatric services, they are better equipped to prepare for the immediate challenges ahead.

Early access to expert lifestyle advice is particularly important. Initially, this is to ensure that infants receive sufficient and appropriate nutrition for growth, and importantly, optimal brain development.

As the child grows, the focus shifts to managing dietary intake to prevent excessive consumption as hyperphagia develops.

Based on our experience in countries where early diagnosis, information, and support are readily available, children with PWS born in recent years have had a significantly better start in life compared to the generation that preceded them. Severe obesity is often avoided in early childhood. These children also tend to develop greater expectations of themselves and a more optimistic outlook for their futures.

5.2.2 Early intervention also has the potential to positively influence the developmental trajectory of children with developmental disabilities.

While 'early intervention' is typically understood as interventions within the first three years of life, in this section, we also address the management of the transition from under-eating to over-eating, which may occur beyond the first three years of life.

Drawing from the wider neurodevelopmental literature and experience of children with PWS, the following three areas were considered of particular importance:

- The early social development of children with PWS
- Structured and informed approaches to behaviour management
- The transition from hypophagia to hyperphagia

5.2.3 Extensive research highlights the importance of enhancing social, cognitive, and functional development through early intervention in the first three years of life for children with intellectual and developmental disabilities.

While a comprehensive review of such benefits is beyond the scope of this Report, the evidence demonstrates that early intervention also significantly improves trajectories of cognitive and functional development and outcomes in later life (Guralnick, 2017 for review).

Intervention early in life for children with neurodevelopmental disabilities are considered important for the following two reasons:

- **Providing support to parents:** Early intervention can address the immediate needs of parents during a highly stressful time, helping them adapt and refine their caring practices to better meet their child's specific needs. This proactive support may also prevent the development of additional secondary disabilities.

- **Taking advantage of developmental plasticity:** Early childhood represents a critical period of developmental plasticity, during which, it is argued, developmental trajectories can be positively influenced. Interventions aimed at enhancing social skills, communication and functional abilities (see Guralnick, 2017) during this time can therefore lead to improvements in subsequent functional, cognitive, and social outcomes.

5.2.4 Preschool interventions are grounded in developmental theory and emphasise various influential factors, particularly the importance of fostering parent-sensitive responsiveness and improving children's cognitive and social outcomes.

These efforts occur within a broader framework that focuses on:

- Improving parental sensitivities and responsiveness to their child's needs
- Facilitating family-orchestrated child experiences that promote learning and engagement
- Ensuring the child's overall health and safety to support optimal development

5.2.5 In PWS, research has demonstrated the feasibility and efficacy of remotely delivered interventions focused on increasing children's social cognition and reducing challenging behaviours through pretend play.

Dimitropoulos and colleagues have developed two targeted interventions: a direct intervention for young school-age children (Dimitropoulos, Zyga, & Russ, 2017) and a parent-training program for families with preschoolers (Zyga, Russ, & Dimitropoulos, 2018).

These interventions use remote symbolic play sessions, such as the application of make-believe scenarios and the use of symbolism. Both types of interventions have been found to be feasible and well-received by children and their parents.

Preliminary results indicate significant improvements in pretend play abilities across the domains of imagination, affect, and organisation. These are skills linked to enhanced cognitive flexibility and fluency in thought (Dimitropoulos et al., 2021, 2022, see also Hödebeck-Stuntebeck, 2012).

5.2.6 Other recent work with school-age children with PWS (Famelart et al., 2022) implemented a train-the-trainer approach, where a child's existing therapist was trained to administer a newly developed intervention.

This project also addressed the geographical challenge of developing behavioural interventions tailored to rare disorders.

Although still in early stages, results show sustained improvement of emotional competencies important for emotion regulation. This may be particularly beneficial as behavioural challenges in children with PWS tend to increase with age.

While the early intervention literature specific to PWS is still developing, these studies offer innovative approaches to addressing the unique challenges of developing behavioural interventions for this population.

5.2.7 In countries where PWS is suspected at birth and accurately diagnosed early in life, there is an opportunity to implement early interventions that not only draw on general evidence and experience but also contribute to developing a PWS-specific evidence base.

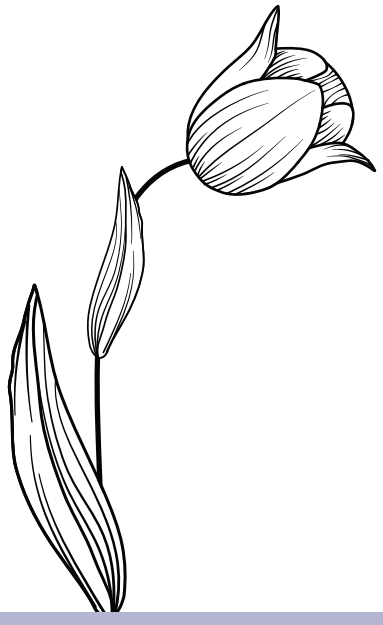
Advances in telehealth offer promising solutions for delivering and evaluating PWS-specific interventions across geographic distances and even international borders.

Early physical interventions, such as starting growth hormone supplementation, which may improve cognitive functioning (Siemensma et al., 2012), and implementing physiotherapy to support motor development also play a critical role in early care.

5.2.8 For children with PWS it remains an open question whether early intervention will result in better outcomes in later life, such as improved social cognition, reductions in challenging behaviours, and having some ability to live in a less restricted food environment without becoming severely obese.

Particularly with respect to managing the effects of hyperphagia, there is a tension between having severe restrictions on access to food that has the benefit of preventing obesity and obesity related illnesses, on the one hand, and, on the other hand allowing some freedoms and choice thereby supporting the person with PWS to learn some level of self-management.

What is essential is regular monitoring so that a plan that is right for that particular child with PWS is developed and if problems arise corrections can be made. Some families report that observation around food is enough; others say that more restrictive approaches are required such as locking food cupboards (see further information on hyperphagia below).



5.3.0 Supporting families to develop informed approaches

5.3.1 As described above, expert opinion underscores the importance of intervention in childhood in shaping positive behavioural outcomes for people with PWS. Such interventions support parents in structuring the home environment and in their interactions with the aim of enhancing the competency of the person with PWS and promoting adaptive behaviours.

However, it is important to recognise that appropriate behavioural support, improving competencies, and the targeted teaching of adaptive skills can lead to meaningful improvements at any age. These improvements extend to not only reducing behaviours of concern but also benefit overall functioning and the quality of life for individuals with PWS.

5.3.2 Among the international group that contributed to this Mental Health Network, differences were present in emphasis and psychological perspectives.

However, there was a general agreement that a comprehensive approach to supporting families in behaviour management and in reducing the likelihood of behaviours, such as emotional outbursts, can be summarised under the following five headings:

- Environmental modifications
- An understanding of the behaviour (in some countries referred to as 'functional analysis')
- Emotional regulation
- Motivation and physical challenges
- Improving the competencies of people with PWS

5.3.3 Environmental assessment and modifications of the support environment should be undertaken and families and other caregivers, in partnership with the person with PWS, should be guided to identify common behavioural triggers or conditions where emotional outbursts or skin picking are more common. This then leads to modification of support plans to mitigate the likelihood of their occurrence and their impact when they do occur.

Interventions may include, but are not limited to:

- Providing both **a food secure environment** (controlling access to food) **and food security** (understanding that food will be provided), to reduce anxiety and food-related behavioural challenges.

- Creating an **enriched environment** that promotes access to meaningful educational, employment, and leisure activities within a positive and supportive social setting.

- Implementing **clear scheduling tools** such as visual indicators for planned events, programming explicit signals for transitions, and providing sufficient time for adjustment (e.g. the use of a visual timer).

- Providing **preventative care** for behaviours like skin picking, by maintaining good physical health and general consistency and fairness in caregiving practices.

- **General education** about other potential risks that might impact their mental and physical health. For example, having contact with strangers through social media and the potential of the harm that could arise seeking food from strangers.

5.3.4 The application of the principles of applied behavioural analysis can result in an understanding of behaviour. These in turn inform interventions. Families can be supported to identify the possible underlying reason or function of behaviours using tools such as Antecedent Behaviour Consequence (ABC) data collection or the Functional Analysis Screening Tool (see Hanley, 2012).

This approach recognises that behaviours, such as emotional outbursts or skin picking, may become a form of communication for that person, i.e. having a 'function'. Understanding the function of specific behaviours can lead to identifying skills deficits and environmental factors that influence the likelihood of such behaviours occurring.

This approach may also identify what are referred to as 'setting conditions'. These are either internal (e.g. the thought of food) or environmental conditions (e.g. noise) that increase the risk of such behaviour occurring.

The following are examples of how such an approach can inform interventions:

- **Understanding the context of the behaviour from the perspective of the person with PWS:** What were they thinking or expecting in the moment? Creating a daily schedule of activities helps alleviate anxiety about what comes next in the day and who will be there to support them.

- **Impaired communication:** People with PWS who lack effective means of communication may use emotional outbursts to express unmet needs. Families and support staff can then be supported to identify and develop appropriate and more effective methods of communication, whether verbal or non-verbal, thereby helping the individual express their needs more effectively.

- **Attention maintained behaviour:** Certain behaviours may be communicating a wish for caregiver attention. Some may be learnt responses, but others may be indicating a need that the person with PWS struggles to communicate. Interventions may include improving communication or providing family members/caregivers with strategies to minimise the giving of attention when managing challenging behaviours, while also maintaining safety and care. This might include, for example, the use of prompt cards or to encourage the use of previously agreed strategies.

- **Improving resilience:** Strengthening the individual's ability to cope can involve early interventions to improve cognition and social understanding. Psychological strategies can also help the person with PWS manage change and their associated anxiousness and learn to adapt to change more effectively (Blackwell et al., 2021).

- **Post incident reflection:** After an emotional episode has resolved and the person with PWS is now calm (often the next day) a period of reflection about the incident may be helpful - 'What do you think we both could have done better'? Writing down what has been agreed may then help the person with PWS process the information and learn.

5.3.5 As discussed in Part 4, there is emerging evidence that people with PWS have an impairment in emotional regulation, possibly due to autonomic nervous system dysfunction.

Teaching and reinforcing emotional regulation skills can significantly reduce the tendency to emotional outbursts. Parents and other caregivers can be supported to teach and reinforce specific strategies that are incompatible with emotional outbursts. When warning signs of a likely outburst appear, agreed-upon interventions should be implemented.

These strategies, developed in collaboration with the person with PWS and those providing support (e.g. family, paid carers, and teachers at school), may include prompting the individual to follow a prearranged coping strategy or employing distraction or de-escalation techniques.

5.3.6 People with PWS may struggle to be motivated, especially in a school setting and during self-care routines.

Physiological factors such as low muscle tone, fine and gross motor deficits, and daytime sleepiness increase the physical effort required to complete basic tasks, necessitating additional external motivation. This may in turn result in disengagement from learning and an increase in emotional outbursts.

- **Interventions:** May include age-appropriate systems of reinforcement such as token economies, behaviour contracts, self-management, and lottery systems.
- **Regular planned activities:** A daily plan of activities that alternates preferred activities (intrinsically rewarding or familiar and practiced activities) with those that are new or challenging. Introducing movement and exercise into the flow of the day helps to increase sensory input that increases breathing and decreases daytime sleepiness.
- **Physical health:** Be aware that conditions such as central or obstructive sleep apnoea may develop and result in excessive daytime sleepiness. Other physical illness might also develop that impact on general well-being and on the person's ability to apply themselves to a task (e.g. hypothyroidism).

5.3.7 Reducing the frequency and severity of emotional outbursts requires a positive partnership between the experts in understanding and managing such behaviours and the parents and other caregivers who will be the experts for the individual with PWS.

Importantly, it requires that practitioners recognise the pressures that parents may face and the importance of matching interventions to what is possible for the family given their specific circumstances.

Further support may be offered to families to help them develop and use objective methods for assessing the efficacy of any intervention, using ongoing data collection (e.g., simple behaviour tracking sheet or diaries) to revise and improve protocols as needed.

5.4.0 Managing the onset of hyperphagia

5.4.1 In early paediatric care for PWS, the primary focus is on addressing feeding difficulties, with augmented feeding introduced if necessary.

As the child grows and approaches the age when hyperphagia is likely to develop (as early as two years and rarely after eight years of age), the focus subsequently changes towards preventing obesity and maintain optimal physical development.

The basic principle is that a caregiver must ensure the child receives a diet that is sufficient and appropriate to support growth and brain development, while avoiding excess intake that could lead to obesity. This is necessary because, for biological reasons, children with PWS lack the ability to regulate their own food intake.

5.4.2 Regular monitoring of growth using length/height and weight centile charts is essential to ensure the child remains on the appropriate growth trajectory, avoiding upward or downward shifts across centiles over time.

Establishing this discipline early lays the groundwork for effectively managing hyperphagia and preventing obesity later on. (Refer to the IPWSO Information Sheet: *Prader-Willi Syndrome and the Younger Child*. www.ipwso.org/information-for-families/new-parents/#younger-child)

5.4.3 There is also hope, supported by anecdotal evidence, that with early diagnosis and access to information, parents can help children with PWS develop a level of self-awareness about their need for support. This may enable them to actively participate in decisions about the level of food control that is required for them to manage their condition effectively.

When an early and accurate diagnosis of PWS is not made and information is not available, the transition from hypophagia to hyperphagia becomes a critical period of risk to the health of the infant and young child with PWS. Severe obesity can develop as families, often initially relieved that their child is finally able to feed, remain unaware of their child's inability to self-regulate food intake.

Early diagnosis, combined with access to information and expert dietetic and paediatric support from health professionals familiar with the needs of people with PWS, can positively impact physical, cognitive, and emotional development. It may also help establish a pattern of effective and sustainable management of the food environment in the future.

It is widely accepted that the development of hyperphagia in early childhood has a biological cause, though the exact mechanisms are not yet fully understood. As a result, the regulation of food intake during the transition from hypophagia to hyperphagia must be managed, at least in part, by someone other than the child with PWS, usually the caregivers.

It is now recommended that caregivers help children with PWS to understand their specific needs and involve them in decisions about food management and exercise strategies from an early age. While there is no research evidence yet to confirm the benefits or drawbacks of this approach in terms of a person with PWS being able to control their own eating behaviour, it represents an important move towards a more personalised and respectful approach to food security (see 5.7 on hyperphagia).

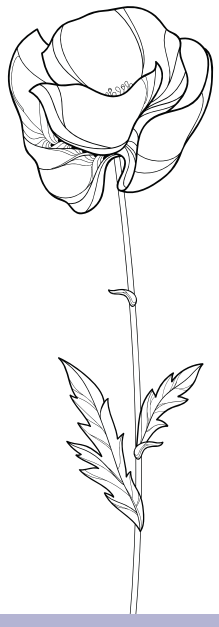
Intervening to enhance well-being

5.5.0 Interventions: General principles and the importance of context

5.5.1 Interventions must be evaluated within the context of the family's immediate environment and the wider social care setting. The availability or absence of support for both the individual with PWS and their family is likely to significantly impact health and well-being.

As illustrated in **Figure 15**, the process of assessment also requires an evaluation of the social and family context. The purpose is to both better understand the factors that may be contributing to the existing challenges and to inform what interventions are appropriate and feasible.

Consequently, interventions should be approached more broadly than traditional medical methods. For example, managing an outburst is often less about using medication and more about equipping families or support staff with the necessary understanding to establish an effective and supportive environment as far as is possible.



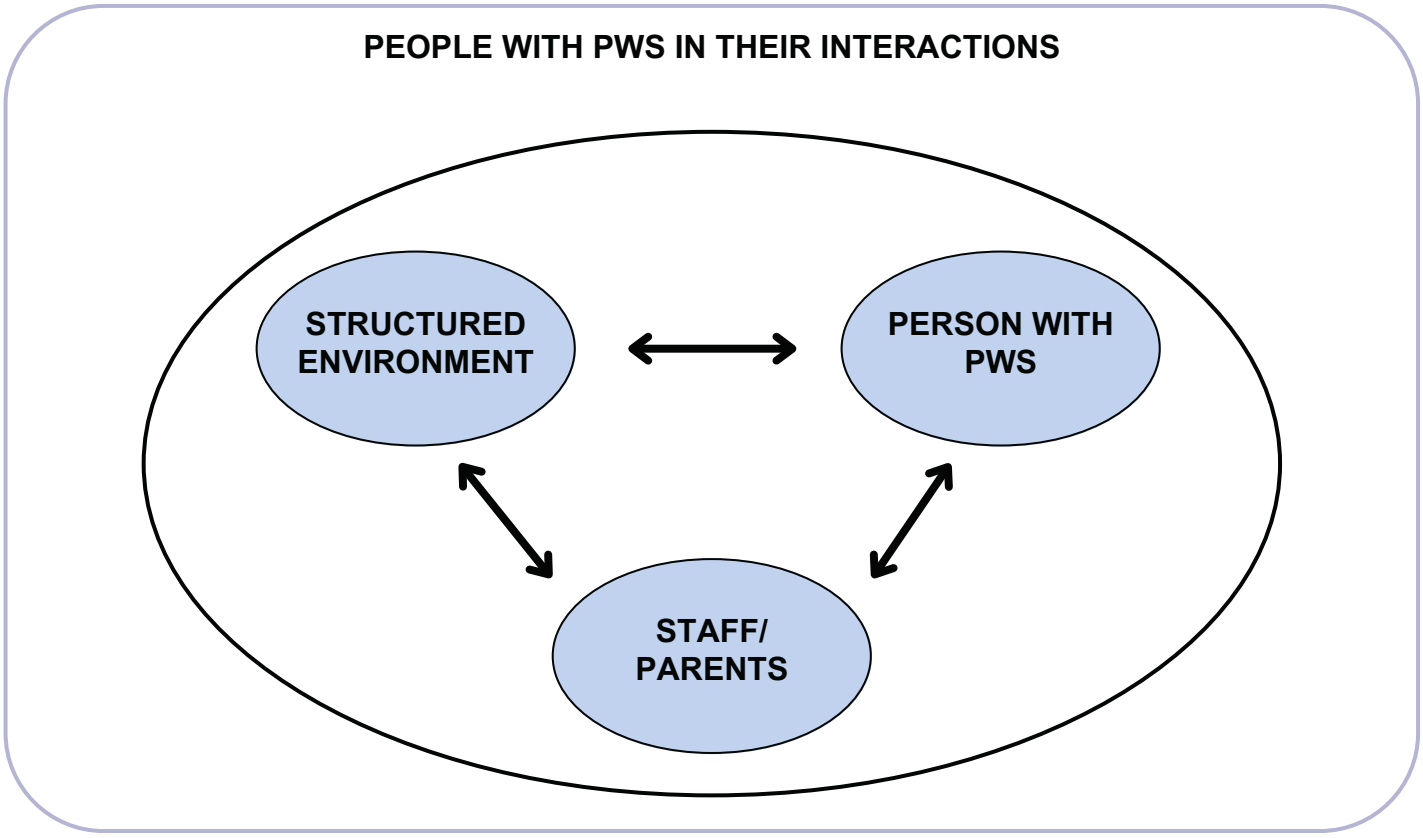


Figure 15 The importance of a systemic perspective. Courtesy of Norbert Hödebeck-Stuntebeck and Hubert Soyer.

5.5.2 Effective interventions are rarely singular or straightforward. Instead, they require a nuanced understanding of the different individual and systemic factors that influence the well-being, quality of life, and mental health of the person with PWS at a given moment.

While research and expert clinical observations are improving our knowledge of the elements that contribute to quality of life, and the unique dimensions of mental ill health observed to impact on the lives of people with PWS, there is much still to be understood.

Although there is reason for optimism, there is also a risk of raising parental expectations to a point where families may feel a sense of failure if challenges persist despite interventions.

Individuals with PWS differ significantly, and strategies that prove effective for one person at a particular time, may not work at another time, or with a different person with PWS.

Services designed to address the behavioural and mental health needs of people with neurodevelopmental conditions must be flexible and responsive, ensuring access to care promptly when it is needed.

Families often juggle numerous responsibilities, including caring for other children, managing work commitments, supporting each other, or, in some cases, shouldering these duties as a single parent. These realities impose practical constraints on family-centred interventions. Similar challenges exist in social care settings for adults with PWS, particularly when individuals share a living environment with others, creating additional complexities.

5.6.0 Targeted interventions for the PWS neuropsychiatric phenotype

5.6.1 People with PWS, families, and professional support providers may seek advice from health services when some of the behaviours commonly associated with having PWS increase in frequency and intensity or when there is a change in a person's mental state or behaviour that is unexplained.

These changes in behaviour or a deterioration in the person's mental health frequently have a major impact on the family and put attending school or college or living in other support environments at risk.

Where a person's behaviour is particularly severe, there may be concerns about the risk to others, and the criminal justice system may become involved.

5.6.2 Interventions are informed by a clear identification of the issues causing concern and an understanding of the various factors that may increase or decrease the nature and severity of the index problem or its consequences. Such observation, in turn informs the support and the nature of the intervention.

Where the frequency or severity of behaviours has markedly changed, the onset of physical or mental ill health must be considered, and if necessary, further observations and investigations undertaken. Under these circumstances, where a co-morbid illness is identified, the intervention is likely to be to treat the co-morbid condition.

Arriving at an understanding of the reason why particular new concerns are now present is invariably very dependent on the observations of those providing support, again emphasising the importance of a collaborative approach.

5.6.3 As outlined in Part 4 on mechanisms, assessment approaches should be informed by biomedical, developmental, psychological, and systemic models of understanding. Each model has its relevance, and in different situations, one may offer greater therapeutic value than others.

While the emphasis may vary and disciplines bring different theoretical perspectives, it is the formulation that aims to articulate the clinical team's understanding of the primary issue that has led to a person with PWS or those providing support to seek help.

5.6.4 Clinicians will be familiar with the multifaceted nature of the assessment process, which varies depending on the reason for the referral and the specific concerns identified either before or during the consultation. The outcome of the assessment is a treatment plan.

Key components of the assessment may include:

- **Comprehensive history:** Gathering personal, developmental, medical, and family history from both the person with PWS and an informant. This includes evaluating whether the developmental history supports a diagnosis of intellectual disability or autism spectrum condition.

- **Behavioural analysis:** A detailed description of the behaviours of concern, including their characteristics (e.g. topography and severity of skin picking, the course and resolution of emotional outbursts), as well as potential internal (e.g. mood) or external (e.g. lack of occupation) conditions that may reduce or increase the likelihood of such problems and/or act as triggers.

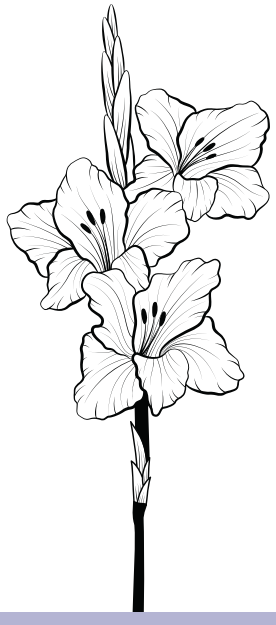
- **Stability of the living environment:** For a person with PWS, the living environment plays a critical role and is often referred to as 'the shadow patient.' This term highlights how the environment silently shapes and supports the individual's well-being. It encompasses essential elements such as food security (knowing that meals will be provided), food safety (ensuring access to food is controlled), and a structured, predictable daily routine that includes consistent activities and exercise. The presence and reliability of parents and caregivers are also vital components. Together, these factors function as an invisible but powerful influence on the person's health and behaviour.

- **Physical and mental state examination:** A physical examination should be conducted if a medical condition is suspected, and a person's mental state assessed, including mood, cognitive function, and the presence of any abnormal mental beliefs or experiences. This is particularly important where a deterioration has been observed from their baseline in their mental state and/or general functioning.

- **Structured assessments:** Evaluating cognitive, social, and functional abilities when indicated.

- **Targeted investigations:** Conducting further investigations as needed, based on history, such as sleep studies or endocrinological evaluations.

- **Longitudinal observations:** Tracking behaviours and mental state over time to identify triggers, environmental influences, and intervention outcomes.



5.6.5 Figure 16 is an example of how formulation can be represented diagrammatically, and how this, in turn, guides intervention strategies.

For example, a person with PWS may be referred because of severe emotional outbursts. These episodes may share characteristics commonly observed in people with PWS.

A thorough history and examination reveal a long history of outbursts, with no indication that they are linked to the onset of a serious mental or physical illness.

With this individual, the outbursts involve verbal and physical aggression, are triggered by minor frustrations, and tend to occur when the person is tired or experiencing a low mood.

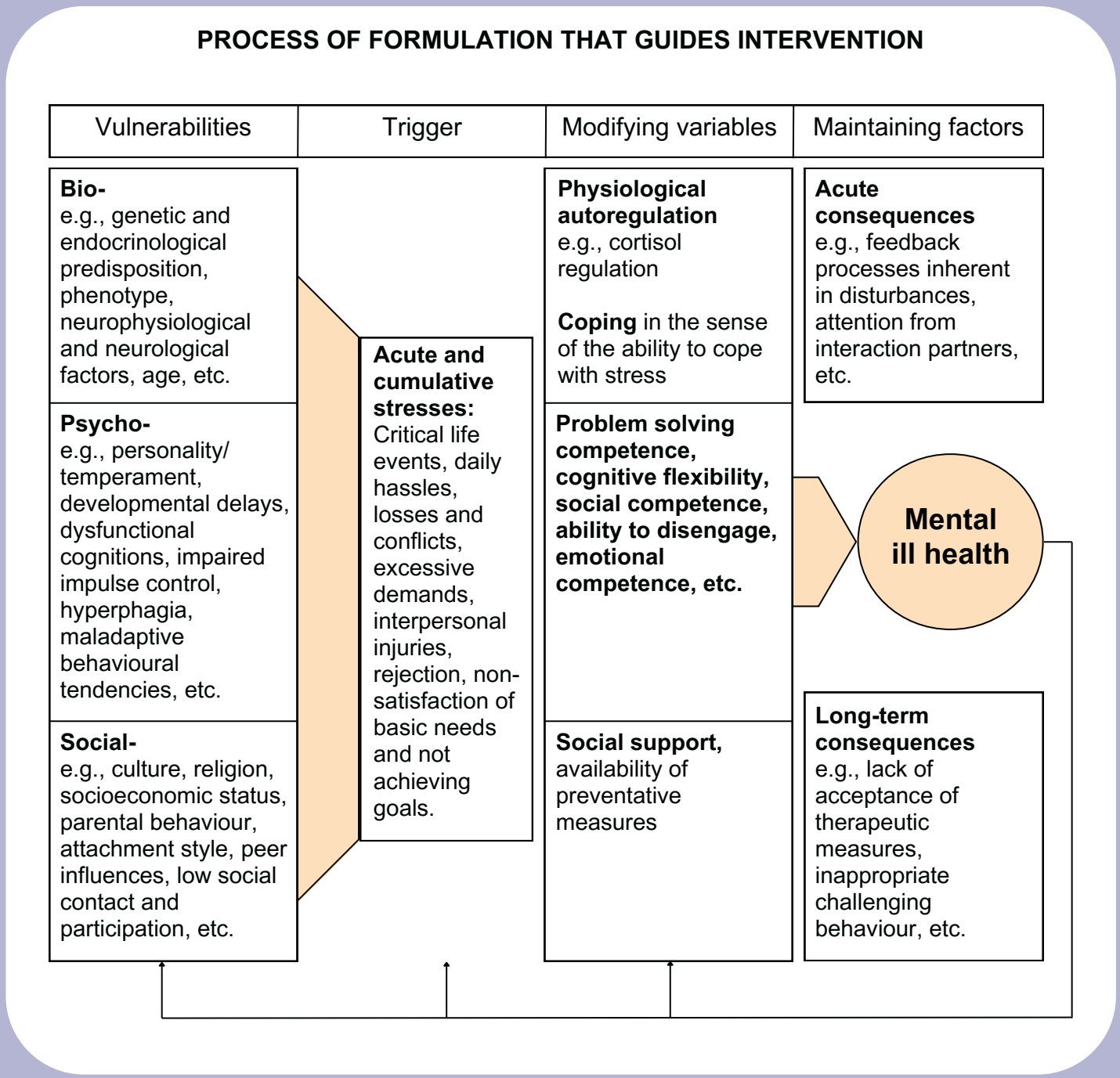


Figure 16 Diagram illustrating the process of formulation that guides intervention, courtesy of Hubert Soyer and Norbert Hödebeck-Stuntebeck.

5.6.6 Different disciplines offer distinct approaches and theoretical perspectives.

As discussed in Part 4, psychological models for understanding behaviour based on learning theory have been very influential. A description of a behaviour alone may have limited predictive value for treatment and may overlook how behaviours develop and become reinforced over time.

A comprehensive formulation emerges from integrating these varied approaches, alongside the insights of families and support providers, into a cohesive understanding of the issue at hand.

5.6.7 The assessment process can be aided using validated and reliable informant-based and direct assessments, designed either for use with people with intellectual developmental disabilities or specifically for people with PWS.

These assessments are particularly valuable prior to an intervention, because establishing a baseline measure of the behaviour of concern, as well as the person's affect and mental state, allows for repeated evaluations over time to determine the intervention's effectiveness.

Examples include the Aberrant Behaviour Checklist (Aman et al., 1985) and the short form of the Developmental Behaviour Checklist (Taffe et al., 2007).

The Foundation for Prader-Willi Research (FPWR) has supported the development of PWS specific assessments, for example, the PWS Anxiousness and Distress Behaviours Questionnaire (PADQ) (Cotter et al., 2023).

Specific applications

5.7.0 Treating hyperphagia and preventing obesity

5.7.1 Until very recently there have been no treatments approved specifically for treating hyperphagia.

A double-blind placebo-controlled trial of an existing medication, topiramate, to treat the emotional outbursts associated with PWS showed no effect on behaviour but a secondary outcome was the finding of a significant effect on hyperphagia (Consoli et al., 2019).

However, in March 2025, Diazoxide Choline Controlled Release (DCCR), now known as VYKAT™ XR, became the first medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of hyperphagia in people with PWS aged four years and older.

Its mode of action is presumed to involve the activation of the K_{ATP} channel in neuropeptide Y (NPY)/Agouti related-protein (AgRP)/gamma aminobutyric acid (GABA) neurons in the hypothalamus. This action would be to reduce secretions of NPY, AgRP, and GABA, which are potent endogenous orexigenic (appetite stimulating) neuropeptides and neurotransmitters, and a reduction in their secretion has the potential to reduce hyperphagia.

5.7.2 The various multicentre trials of what was then called DCCR included a blind placebo-controlled phase, an open phase, and a blind withdrawal phase, followed by another open phase. The U.S. Food and Drug Administration (FDA) approved the medication based on findings from these different phases.

VYKAT XR is now available and is being prescribed for people with PWS in the USA albeit at a high cost. While the FDA was satisfied that the efficacy and safety data justified the approval, what remains to be seen is the effectiveness of the medication in the real world.

In the trial not every participant responded, and we do not know whether those that showed a reduction in scores on the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) will be able to live in a less food restricted environment without risk of hyperphagia and resultant obesity.

In addition, the medication has the effect of increasing blood glucose levels and may give rise to excessive growth of body hair.

Although the approval of this medication is a favourable development, it is essential to carefully assess the extent of its effectiveness.

5.7.3 We anticipate that it will be some time before this medication will be available in other countries, and there is concern that the cost will be prohibitive.

In addition, for this medication to become available globally, it will have to be approved by other Regulatory Authorities and funding for the treatment agreed by each country.

Other agents for the treatment of hyperphagia targeting different biological pathways are either in clinical trials or expected to be studied in the future (Mahmoud et al., 2023).

For these reasons, interventions for hyperphagia still need to focus on preventing the consequences of hyperphagia, that of severe and life-threatening obesity. This is achieved through supporting the person with PWS to maintain a healthy diet and body weight, through the presence of a food secure environment and food security and establishing a structured daily routine that includes adequate and appropriate levels of exercise.

As outlined below, the exact nature and extent of the food security measures need to be tailored to the severity of the hyperphagia.

5.7.4 Reports from families and published studies observing the eating behaviours of adults with PWS indicate that the ability to regulate food intake varies significantly among individuals with the condition (Holland et al., 1993, Lindgren et al., 2000, Zipf et al., 1987).

Similarly, the age in childhood when hyperphagia becomes evident also differs (Goldstone et al., 2012, Miller et al., 2011). For these reasons, instead of adopting a rigid ‘all or nothing’ approach to controlling the food environment, the degree and method of food access management should be tailored, based on an understanding of the individual.

5.7.5 Restrictions on food access can, according to need, range from more stringent measures, such as locking food cupboards and kitchens and maintaining total control over the food environment, to less restrictive approaches, such as setting clear rules and ensuring supervision when the person with PWS has access to food.

The benefits of effectively managing the food environment extend beyond obesity prevention and include reduction in levels of anxiousness and in emotional outbursts related to food. The primary aim of an individualised diet plan is to regulate energy intake to match the body's energy demand.

However, food security encompasses more than just limiting access to food and has been defined as:

A totally supportive environment surrounding a person with PWS that helps alleviate anxiety related to hyperphagia by: limiting access to food in all settings when it is not time for meal or snack; avoids meltdowns by clear expectations about what and when they will eat; keeps them on a set meal/snack schedule with few exceptions; keeps them busy and engaged with activities and social connections that don't revolve around food; and understanding that hyperphagia in PWS is managed, not cured. If food security is working, it results in stable weight, few opportunities for food stealing, fewer meltdowns and arguments about food.

Definition courtesy of
Elizabeth Roof

FOOD SECURITY is no doubt, no chance, no disappointment - I know what I will eat, when I will eat it, and what portion size I will have. FOOD CONTROL is that I also know I will not have access to food at any other time. Under these conditions, I am content.

Definition courtesy of
Janice Forster

5.7.6 While people with PWS may at times challenge the need for food security, hyperphagia has been reported to be of great concern to them (Dykens et al., 2022).

Those providing support will also describe how people with PWS embrace the rules put in place to manage access to food and can be angry if a family member or professional support staff does not adhere to them.

5.7.6 There remains some disagreement among those in the group as to the extent to which people with PWS should be allowed to have control over their own food environment. Experience indicates that, while some individuals may manage with minimal oversight, others with PWS risk severe and life-threatening obesity without strict supervision.

This variation in severity of hyperphagia may be partly explained by differences in the brain, particularly in the size of the hypothalamus (Brown et al., 2022). Background genetic influences and early life experience may also be important.

At present, the advice is that if food security rules are loosened it is critically important to monitor weight and to have strategies in place to reintroduce them if serious and consistent weight gain is observed.

5.7.8 In countries where support and access to health expertise is limited, the application of clear rules regarding food access and a structured schedule around mealtimes is recommended. This provides a sense of food security for the person with PWS.

There is now good data collected across different countries that demonstrates that such food managed environments have very positive outcomes that enable people with PWS to have purposeful lives (Hughes et al., 2024).

In countries where there is a greater level of resources and expertise available the support strategy implemented may be more nuanced enabling work with the person with PWS to make some decisions around food and learning from their experience.

With the development of new treatments for hyperphagia it is possible that the drive to eat will be diminished. If this proves to be the case a more flexible approach may then be more possible and more likely to be successful. The process and results of such an approach need to be evaluated and measured.

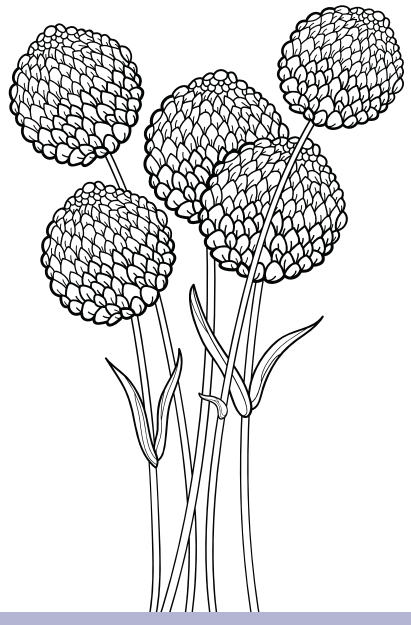
During childhood, parents have a duty to act in their child's best interests. For the parents of a child with PWS this includes parents understanding that their child has an impairment in brain function that results in hyperphagia. Parents and others providing support need guidance about how to compensate for this by providing external controls on access to food.

Childhood is also a crucial period for helping children with PWS develop an understanding of their strengths and challenges. They should be guided to accept and to value external food controls for maintaining their health and optimising their quality of life and life expectancy. Establishing this foundation early can support the continuation of a consistent approach to food security, first at school and then later in adulthood when increasing independence may heighten the risk of over-eating, leading to severe obesity.

The need for food security and a food secure environment in adulthood must be based on an understanding of the particular biological impairments associated with PWS. These impact the ability of people with PWS to match food intake to energy needs. Unrestricted access to food is highly likely to lead to severe obesity, heightened anxiousness, weight related physical illnesses, reduced mobility and quality of life, and, ultimately, early death.

Concerns were expressed in the group that such an ‘all or nothing’ approach to restricting access to food, such as locking food cupboards and the kitchen door, does not allow the person with PWS to learn some level of self-control over food intake. In addition, it does not allow the severity of the individual’s drive to eat to be identified and taken into consideration. It is argued that a too rapid and severe implementation of restrictions results in a self-fulfilling prophesy and the person will lead their lives without having the opportunity to demonstrate what would have been possible with the right guidance. At present there is no published research that has investigated the extent to which people with PWS can learn some degree of control over their eating behaviour. Interestingly, there are anecdotal reports of people with PWS being able to comply with fasting during religious holidays but that is usually in the context of strong group pressure.

Ideally, the negative outcomes reported with unrestricted access to food can be prevented through proactive measures. However, when crises arise and weight increase is severely impacting a person’s health and quality of life, solutions must be identified in accordance with the national laws. At such times, individual rights may appear to be in conflict. However, what is truly at stake is the fundamental right to a healthy and active life – one that enables the person to pursue their goals while safeguarding their well-being.



5.8.0 Targeted interventions for behaviours of concern and psychological issues

5.8.1 There was a consensus that emotional outbursts in people with PWS arise because of a biologically determined vulnerability to such outbursts, possibly because of impaired autonomic nervous system function, combined with the influence of past and present environmental factors that may reinforce and shape such behaviours.

The frequency of emotional outbursts, when they occur, their severity, and their length are strongly influenced by the environment. The way others have responded to these outbursts, both in the past and present, significantly shapes how they manifest over time.

As illustrated in **Figure 17** such outbursts often have a characteristic course, and exactly which intervention is needed and whether an intervention is likely to work will critically depend on the point in the cycle interventions are tried.

As the outburst progresses cognitive competence deteriorates and the chance of the person with PWS being able to control the outburst diminishes.

5.8.2 Having a strategy in place for how to respond when it becomes apparent that someone with PWS is becoming upset is a key part of good support. Such strategies should be developed with the person with PWS when they are calm and be agreed by all concerned.

Examples include prompting the person with PWS to go to a designated area to calm, to listen to something that is associated with calming, undertake previously rehearsed exercises, watching a designated TV show that has been chosen for this person etc.

Food should not be used as part of such strategies.

The advantage of such an approach is that the person with PWS and those providing support immediately know what to try in when in a challenging situation that requires a rapid response from those concerned if it is going to be successful.

While it is unlikely to stop all outbursts it has the potential to reduce their frequency and it engages the person with PWS in a positive way in the task of managing their behaviour.

The person with PWS may not easily generalise such an approach to other settings but family members, care staff, and others can work together to ensure that such an approach can happen in all settings.

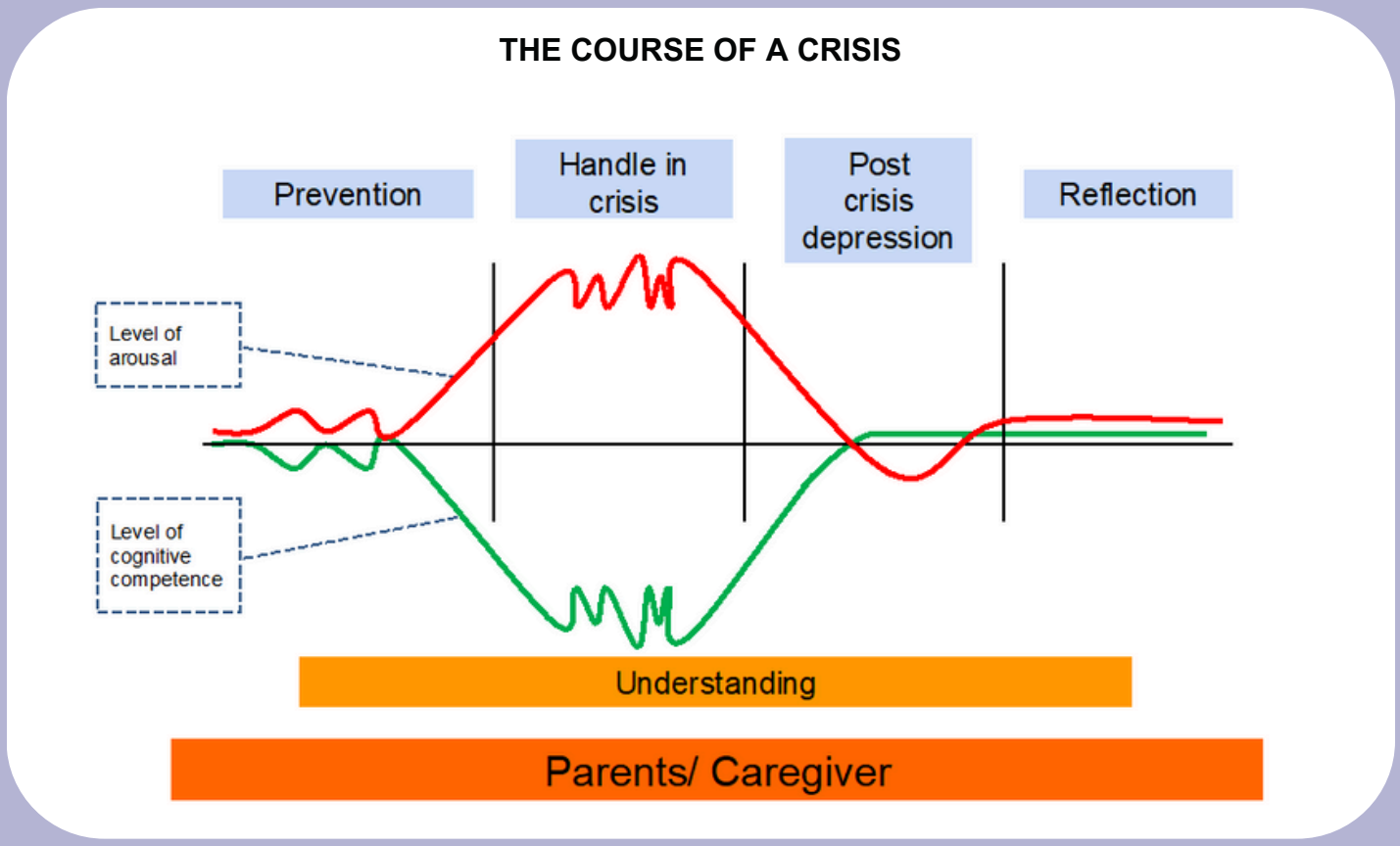


Figure 17 Different stages of intervention in the management of challenging behaviour. Courtesy of Norbert Hödebeck-Stuntebeck and Hubert Soyer.

5.8.2 Earlier in Part 5, various strategies were discussed that might reduce the risk of emotional outbursts during childhood. Many of these preventative approaches also apply in later life. However, outbursts may still occur, and if they are frequent and/or severe, they have a major impact on the quality of life and safety of the person with PWS and family or professional care providers.

Where a person is presenting with persistent and severe emotional outbursts, the initial assessment will guide any interventions and highlight the need for additional data or investigations.

Based on the findings an intervention plan can be developed, ideally in partnership with the person with PWS those providing support. Based on the assessment, the task is to establish the likely factors that are predisposing to, precipitating, and maintaining the emotional outbursts, and the conditions under which they are most likely to occur.

Develop a support strategy in partnership with the person with PWS and those providing support in the phase of reflection, the aim of which is to reduce the likelihood of such behaviours occurring. The strategy must be based on an understanding of the circumstances and must be ethical, acceptable, and feasible, and its impact evaluated by data collection before and throughout the intervention as far as is possible.

Caregivers need to be aware that the person with PWS may not being able to understand the reasons for some change in routine, they may have different expectations of an event than those of the caregiver, and/or the person with PWS may feel unfairly treated. Using visual aids, understanding the communication skills of individuals with PWS, and employing familiar strategies to manage change or the unexpected can reduce and control outbursts.

Establish, in the phase of reflection, with the person with PWS and those providing support, a plan for how to intervene when the person with PWS or those providing support observe that circumstances are likely to arise that are known to trigger an outburst, or when the person's behaviour indicates an outburst is developing.

5.8.3 This approach is illustrated by the 'PWS intervention pyramid' diagram developed by Janice Forster (see **Figure 18**). A detailed example is summarised in the diagram prepared by Kasey Bedard and Annette Griffith (see **Figure 19**).

The 'PWS intervention pyramid' illustrates the point that the cognitive and behavioural phenotype of PWS are best managed by a foundation of environmental supports including a scheduled meal plan with food security and restricted food access, a plan for daily activities, regular exercise, opportunities for sensory experiences, low expressed emotion by caregivers, and clear behavioural expectations (PWS Best Practice Guidelines, 2010, www.ipwso.org/pws-information/information-for-professional-caregivers/best-practice-guidelines-for-residential-care/#PDF).

If emotional and behavioural symptoms emerge then coping strategies can be taught to address them. If symptoms persist despite enhanced coping, additional incentives or behavioural plans may be required.

5.8.4 The use of medication is at the peak of the intervention pyramid and there was a general agreement that psychiatric medications have a limited role to play in the treatment of emotional outbursts, and where they are used it should only be in combination with other psychologically informed intervention.

An exception would be if there was evidence of the onset of a psychotic illness as indicated by the person presenting with an unusual and sudden change in behaviour, the abnormal mental state persisted, and was associated with the onset of abnormal mental beliefs and experiences (see below).

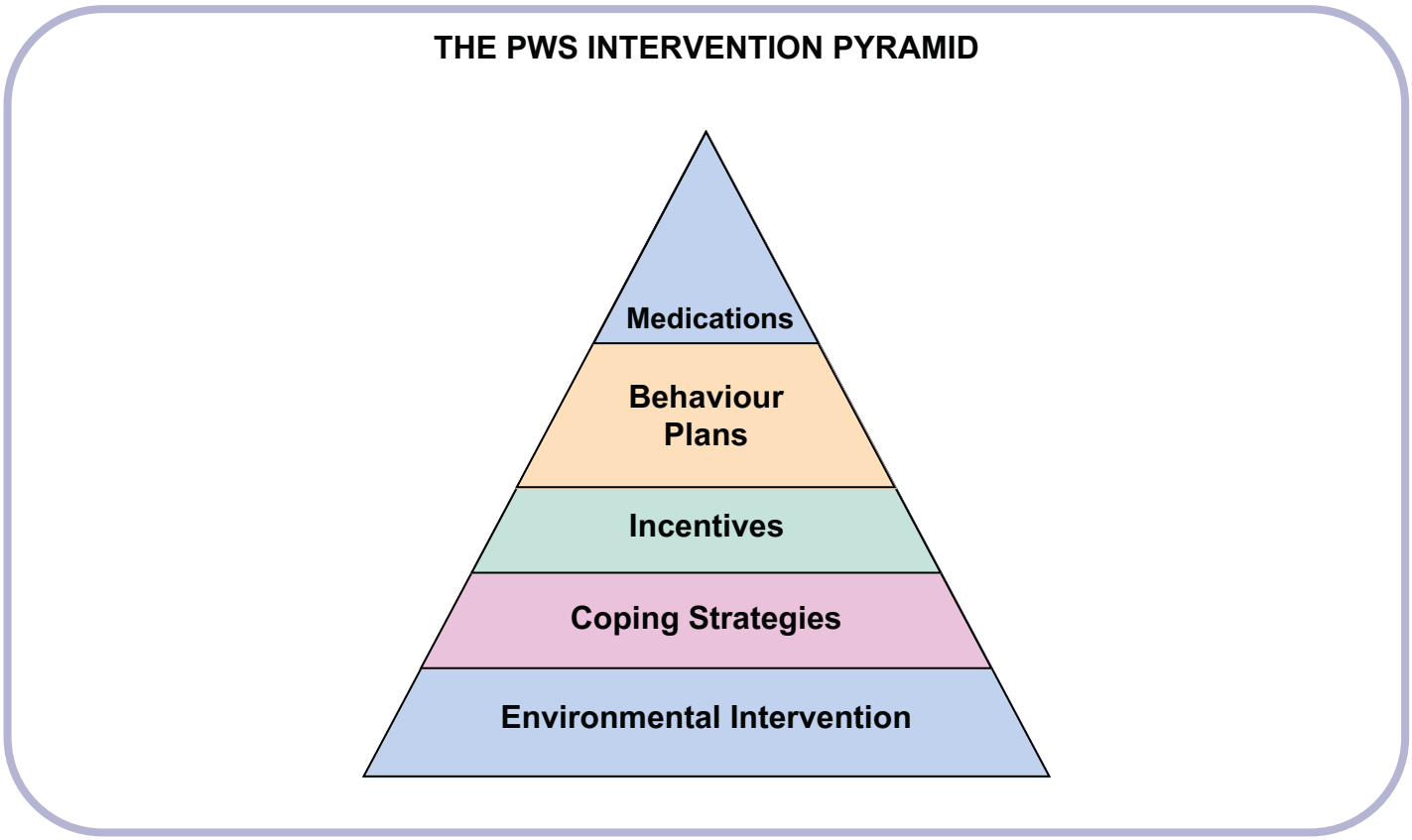


Figure 18 The PWS Intervention Pyramid. Courtesy of Janice Forster.

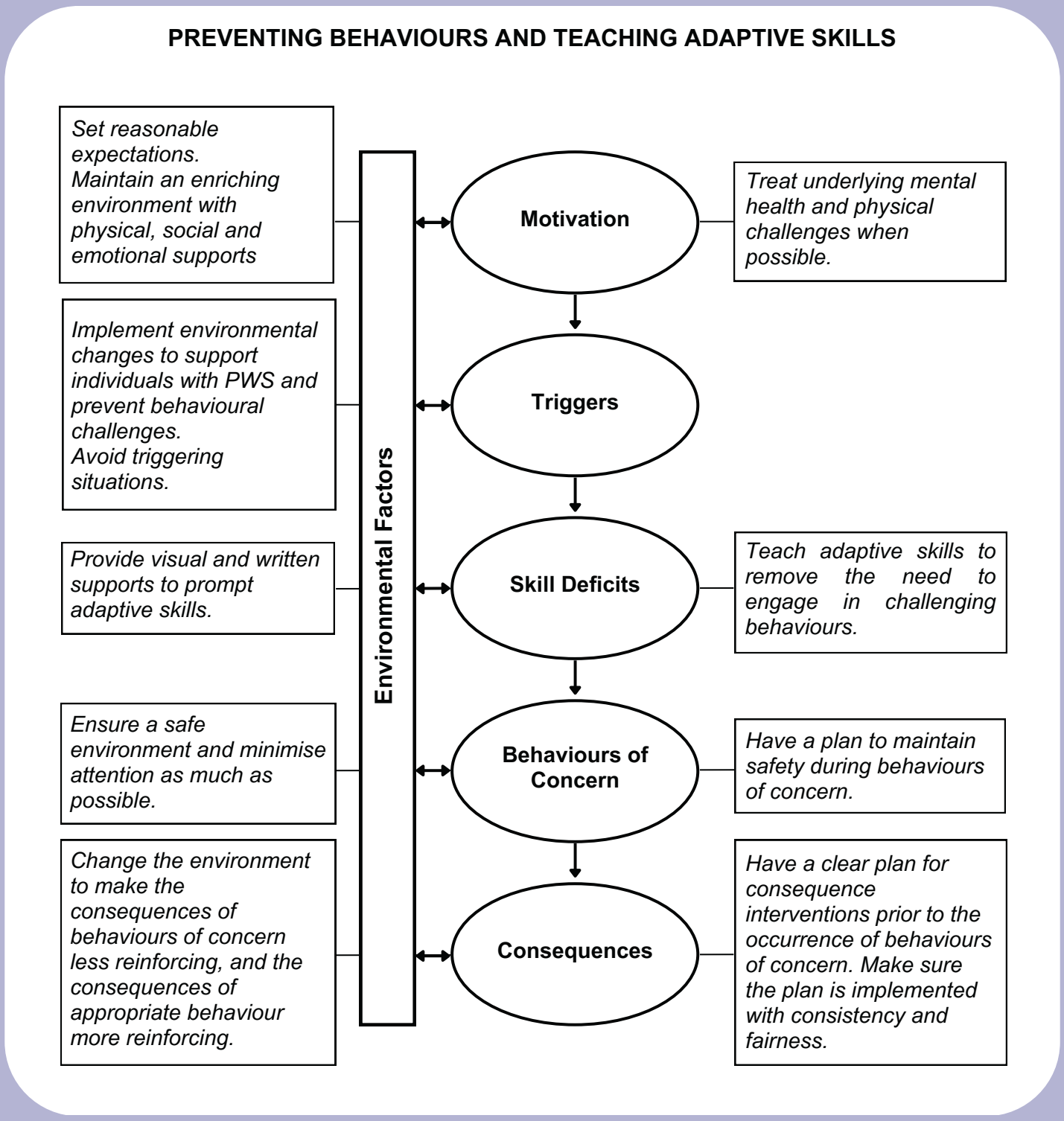


Figure 19 Diagram illustrating different forms of intervention. Courtesy of Kasey Bedard and Annette Griffith..

5.8.5 Medication and vagus nerve stimulation have been explored as treatments for emotional outbursts in individuals with PWS. As described above, the evidence supporting the effectiveness of psychiatric medications in this context has been limited (Rice et al., 2018).

More recently, there has been some more positive evidence, but only one controlled trial. One case note study reported findings from 14 people with PWS, aged from 16 to 51 years, who had significant outbursts. Of these, 13 had show a reduction in both the frequency and severity of behaviour following treatment with the selective serotonin reuptake inhibitor (SSRI), sertraline at low doses (Deest et al., 2021).

Two further retrospective case note studies, one involving the use of aripiprazole, (Deest et al., 2022), and the other risperidone (Durst et al., 2000) also reported some benefit. In the case of aripiprazole excessive daytime sleepiness was reported as a problem. However as these were not placebo controlled trials the influence of placebo effects cannot be ruled out.

5.8.6 In the case of the use of SSRIs, the authors of the above study suggested that this supported the hypothesis that the serotonergic system may play a role in impulse regulation. However, there is concern about the use of SSRIs in this population due to the risk of behavioural activation or triggering hypomanic episodes. Therefore, lower than normal starting doses and slow and gradual dose increases are recommended.

5.8.7 Guanfacine (GXR), a centrally acting alpha$_{2A}$-adrenergic receptor agonists used to treat attention deficit hyperactivity disorder (ADHD) has also been evaluated for the treatment of emotional outbursts in a randomised, fixed-flexible dose placebo-controlled clinical trial. The assessed symptoms included aggression, irritability, inattention/hyperactivity, and skin-picking.

GXR treatment was reported to lead to global improvement in symptoms, particularly those related to behavioural disturbance in people with PWS. Specifically, GXR was found to reduce aggression and hyperactivity in this population. Additionally, there are possible beneficial effects on skin picking behaviour.

Fatigue was the most common side effect, but overall daytime sleepiness was no worse than placebo. There were no serious adverse effects reported. GXR did not lead to any change in weight, heart rate, blood pressure, or cardiac rhythm, compared with placebo.

The results of this clinical trial suggest that GXR is an effective and relatively safe treatment modality for behavioural problems in people with PWS (Singh et al., in submission).

5.8.8 Two small open label trials of vagus nerve stimulation, one using implanted stimulators and the other using transcutaneous vagus nerve stimulation, reported significant improvements in behaviour after some months of stimulation using protocols approved for the treatment of epilepsy (Manning et al., 2016, 2019).

In the first trial involving three participants with PWS, the aim was to study the impact of vagus nerve stimulation on hyperphagia. While no effect on hyperphagia was observed, two of the participants with PWS and their families reported very significant improvements in behaviour, thus leading to the second trial.

A large multi-site trial is now ongoing in the USA. As part of the large trial of DCCR as a treatment for hyperphagia described earlier, it was reported that aggressive behaviour also reduced (Strong et al., 2024).

As new treatments for hyperphagia are evaluated, it will become clearer whether effectively managing hyperphagia also leads to improvements in emotional outbursts.

There was a consensus that, in the absence of any co-morbid mental illness (e.g affective disorder or psychotic illness), the use of psychiatric medication by itself is of limited value. If it is to be used it should be based on a full understanding of the behaviour and following the application of psychological interventions and environmental modifications. To judge an intervention's efficacy, it is important to collect baseline data on behaviour rates and severity.

Early observations of the use of specific medications and of vagus nerve stimulation provide evidence that these might bring benefit. The assumption is that they will improve emotional regulation, thereby enabling people with PWS to better regulate their behaviour. In addition, observations from the DCCR trial indicate that if hyperphagia is treated, behaviours such as emotional outbursts may also improve.

5.9.0 Self-harming behaviours: Prevention and intervention

5.9.1 Self-harming behaviours focused on the body, such as skin or rectal picking, can be particularly challenging to manage because of the difficulty in preventing access to wounds.

As discussed in Part 4, the general conclusion is that having PWS is associated with a vulnerability to such self-harming behaviour. The reasons for this are unclear but one factor may be the increase in pain threshold and therefore the lack of negative feedback. However, it is also clear from detailed observational studies under different conditions that environmental circumstances play an important role (Hall et al., 2014.)

Skin picking is much more likely to occur under conditions where the person with PWS is alone, or is with others but being ignored.

As with emotional outbursts, interventions are aimed at prevention and at treatment when picking occurs. Interventions focus on understanding the factors that trigger, sustain, or prevent self-harming behaviour.

5.9.2 Prevention can include keeping the skin as comfortable as possible by minimising irritation. This may involve preventing insect bites, keeping skin moisturised and free of acne, if possible, and ensuring that any existing wounds are kept covered and treated according to medical recommendations.

As scars can often become the source of irritation and new sites for picking, applying thick ointments to ensure that scars remain moisturised is important. Similar ointments can be used on cuticles and nail beds if those are common sources of irritation.

If lips are a common location for picking, using salt scrubs or other exfoliants to remove dead skin, combined with lip masks (which are often superior to lip balms), can help maintain moisture and prevent further irritation.

Keeping fingernails short can also reduce the ability to pick at skin.

5.9.3 Some people with PWS may resist the covering and treatment of wounds. In such cases, reinforcement strategies can be used to incentivise wound coverage and encourage dry wounds (wounds showing no signs of new picking) when standard wound treatment is not sufficient.

It is generally advisable to avoid reinforcing the absence of picking itself. Drawing attention to the behaviour through frequent reminders may have the counterproductive effect of increasing picking if those affected can identify this as a point of frustration for caregivers.

5.9.4 A preventative approach, in addition to focusing on the skin as described above, should examine the environmental circumstances during which self-harming behaviours occur.

Where the evidence suggests that specific times of the day when there is limited activity are particularly problematic, identifying activities that are engaging and potentially incompatible with skin picking for these times may bring benefit.

Activity with the hands, such as computer games, knitting, or undertaking a particular hobby such as model making, are examples that have been reported to have been used.

5.9.5 As with emotional outbursts, there is conflicting evidence from open label trials, case reports, and retrospective case reviews of some benefit of medications for the treatment of self-harming behaviours.

Anticonvulsants, particularly topiramate (Shapira et al., 2002), the nutraceutical agent N-acetylcysteine (Wieting et al., 2021), SSRI anti-depressants (Bloch et al., 2001, in the non-PWS population), and guanfacine (Singh et al., 2019) have all been tried with variable effects (see review by Whittington & Holland, 2020).

The general opinion is again very similar to that for emotional outbursts. There is a potential limited place for medication use but only in the context of other approaches as described above – see also the PWS Intervention Pyramid (**Figure 18**).

The relationship between obsessive symptoms and self-harming behaviour is uncertain. Self-harming behaviour may be worse in the presence of depression and the careful use of anti-depressant medication may be indicated (at low dose) where depression is present and persistent.

Self-harming behaviours in the form of skin picking are common in people with PWS, and interventions to reduce their frequency and severity should be based on an understanding of the behaviour and the identification of the factors that predispose to, precipitate, and maintain the behaviour and the settings conditions under which it is most likely to occur.

Where skin picking is present, the approach should be one of preventing and reducing the likelihood of the self-harming behaviour through good skin care, informed interventions, and changes to the support environment.

The effects of several classes of medications have been tried, mainly in open label trials, with mixed results. Careful treatment of co-morbid psychiatric conditions, such as depression, may be indicated together with other intervention strategies.

Where self-harming behaviour is severe and resistant to environmental changes and psychological interventions, a trial of medication such as N-acetylcysteine may be indicated. The potential benefits, risks and limitations of interventions including medications should always be systematically studied, and if no benefit is observed, the treatment approach re-evaluated.

5.10.0 Approaching disturbances of mental state: Affect, anxiousness and major mental illness

5.10.1 The conditions described in this section are primarily characterised by the presence of disturbances in affect (mood), emotions and feelings that are of sufficient severity to impact, to varying degrees, on the well-being of the person with PWS and on their ability to function.

Examples include feelings of severe anxiety, disturbances in mood that include both depression and a heightened mood state, referred to as hypomania or, if more severe, mania, or atypical psychotic illness. The last may manifest as a change in the way someone appears, behaves, or communicates with others, together with the onset of specific mental symptoms.

These disturbances of mental state are different from what we have called 'behaviours of concern', as is their treatment.

We consider the treatment of the following:

- Anxiety (referred to as anxiousness)
- Affective (mood) disorders
- Atypical psychotic illness

5.10.2 As described in Part 4, it remains uncertain whether what is frequently referred to as anxiety in people with PWS is the same as might be diagnosed as an anxiety disorder in the typically developing population. To make a distinction from anxiety as used for the typically developing population, we have instead used the term 'anxiousness'.

Such feelings of anxiousness are often present in specific situations or at moments of change or uncertainty. This is different from the characteristics of a generalised anxiety disorder, where anxiety may be present across all settings, and it is also different from anxiety that relates to a particular situation or object, as is the case with a phobia.

Anxiousness may also be a key aspect of the pathway to an emotional outburst and therefore its management can overlap with strategies that aim to both prevent and effectively manage such outbursts.

Preventing and managing anxiousness affecting people with PWS should be based on an understanding of how it affects an individual, but the following four components are likely to be relevant:
affects an individual, but the following four components are likely to be relevant:

- Ensuring that there is an **agreed strategy of food security** in place, thereby eliminating uncertainty about mealtimes and when or if food will be available.

- **Establish a routine and structure to the day** using visual aids, such as timetables, clocks, and calendars, to enhance understanding of time and when activities will take place and thereby reduce the unexpected.

- **Psychologically informed strategies** can help individuals and their caregivers manage anxiety, whether anticipated or triggered by unexpected change. These may include prompt cards and pre-agreed plans.

- Where anxiousness is more pervasive and resistant to the above measures, **the use of medication may be considered** (see section on medications).

5.10.3 For someone with PWS the treatment of affective disorder or serious mental illness, such as a psychotic illness, starts with identifying the presence of the disorder, ensuring an accurate diagnosis.

As described in Part 4, such illness presents with changes in a person's mental state that may include abnormalities of mood, apparent confusion and difficulty thinking (thought disorder), and the onset of abnormal mental beliefs and experiences (delusions and hallucinations) (see Soni et al., 2007, 2008, and Aman et al., 2024, for review).

People with PWS may present with a clinical picture that is characterised by depressive or hypomanic mood swings. These mental phenomena may vary in intensity but persist over time. They are different from the clinical picture that characterises the usually brief emotional (temper) outbursts associated with PWS and are instead a manifestation of the onset of a co-morbid mental illness.

The choice of psychiatric medication for treating persistent and/or recurrent abnormal affective states depends on individual circumstances. Where there is clinical evidence from the history of recurrent depressive, hypomanic, or mixed affective states or of bipolar illness, determining the most appropriate intervention will depend on the individual circumstances.

The general principles of treatment are as follows:

- **Assessment:** Confirm whether there is a history of affective disorder and its characteristics and the extent to which it persists over time and has an impact on the person's ability to function and on their quality of life.
- **Identify and address triggers:** Establish whether a specific reason can be identified that might explain a deterioration in affect, such as changes in support practice, loss of a loved one, or neglect and abuse. Where such potential triggers or causative factors are present, these should be addressed. This may include re-establishing previously accepted support strategies (including food security), and psychological interventions for grief etc.
- **Support and risk:** Assess the level and type of support needed, especially regarding risks of suicide, self-harm, or other potentially harmful behaviours – for example repeatedly running away, refusing support, or self-neglect. Where such risks cannot be mitigated in the family home or in other support settings, consider whether increased support can be provided in the short term to manage such risks.
- **Medication for persistent symptoms** Where the diagnostic characteristics of an affective disorder are persistent and are of a severity to impact on the person's functioning and/or their quality of life, consider the use of pharmacological treatments based on the diagnosis. Care must be taken with use of antidepressant medication, particularly if there is also a history of hypomanic or manic mood swings. Medications, such as the selective serotonergic reuptake inhibitors (SSRIs) can result in mood swings from a depressed to a hypomanic mood state or lead to a general deterioration in behaviour
- **Treat mood diorders:** When hypomanic states, bipolar disorder, or signs of developing affective psychosis are present, antipsychotic and/or mood stabilising medications are likely to be the first line of treatment.

5.10.4 Affective symptoms, as described above, may be accompanied by the development of abnormal mental beliefs or experiences or other features indicative of a possible psychotic illness.

The onset of a psychotic illness can be acute and have a major impact not only on the person with PWS but also on those providing support.

This is particularly the case with the first episode, when there is likely to be very limited understanding as to what is happening or how to manage the situation.

5.10.5 When there is a marked and persistent change in a person's mental state and behaviour, it is essential that those providing support seek urgent guidance from healthcare professionals who have the necessary expertise. That may initially be in the Emergency Department and may lead to urgent psychiatric referral (see section on services below).

The most immediate task is to identify the likely explanation of this marked change in behaviour and mental state, and to start the most appropriate intervention.

Where a psychotic illness is identified, the general principles of treatment are as follows:

- **Build shared understanding:** Working with the person affected and their family and/or professional carers to ensure that there is an agreed understanding of the presenting problem.
- **Confirm diagnosis:** On assessment, confirm whether the explanation of the observed change is the onset of a psychotic illness, excluding those physical illnesses, such as delirium, or any other cause that might present similarly. The diagnosis of psychosis is not made by just eliminating the likelihood of physical illness but also by evidence from the history and mental state examination that establishes the presence of such an illness.
- **Assess risk and support needs:** Evaluating the risk of the person with PWS to themselves or others and ensuring that the necessary support is available. Extra support or admission to hospital may be required depending on the severity of their psychiatric illness and the ability of family and/or professional support staff to continue to support them at home.
- **Appropriate medication treatment:** Start treatment of the psychotic illness with appropriate anti-psychotic medication and, if the clinical state indicates, consider the careful use of antidepressant and/or mood stabilising medication. Start at a low dose and only increase slowly if clinically indicated, reviewing regularly.
- **Start low, go slow:** The general rule when prescribing psychiatric medication to people with PWS is to start at a low dose and increase slowly only if required. Note that individuals with low lean body mass often require lower doses than their age-matched peers. It is important to avoid side effects as this can lead to the rejection of an otherwise effective medication.

- **Maintain food security:** It is important to keep the usual food security/food control measures in place. Not all medications for psychiatric illness that increases appetite and cause weight gain in the general population will show the same in people with PWS but having controls in place will ensure that any tendency to weight gain associated with medication use will be managed.

- **Manage risk and monitor health:** Ensure that an appropriate care plan is in place to manage any identified risks, including the risk of self-harm, suicide, or harm to others. The regular monitoring of physical state, including liquids and nutrition, and ensuring the maintenance of food security as required. Where possible provide a quiet, structured, and relatively undemanding environment that can adapt as the person's mental state improves.

- **Provide long-term follow-up:** Evaluate ongoing medication use and address any unmet support needs. There is limited data on the length of time a person with PWS should remain on psychiatric medication after recovery (see Larson et al., 2014). Our advice is to follow national or international guidance on the treatment of psychosis in the typically developing population and continue to regularly follow up, particularly if drug withdrawal is being considered.

- **Ongoing community support:** With recovery, establish a longer-term support plan at the family home or in other community settings to ensure that knowledge about the recent illness is available and that the person's mental state is monitored and advice is obtained in the event of a suspected relapse.

Meeting the mental health needs of children and adults with PWS

5.11.0 What should services look like?

5.11.1 To address the broad, higher-level issues that impact well-being and quality of life, we have made recommendations earlier in Part 5 based on the literature and on the experience of those working in health services, professional care providers and parents.

These recommendations and stated goals are relevant to meeting the needs of people with neurodevelopmental disabilities generally, not just to people with PWS. However, there is the additional need for a deep understanding of the syndrome if adequate services are to be provided and the principles set out earlier in **Figure 14** are to be adequately met.

5.11.2 We recognise that implementing these measures for any country is likely to be an ongoing process, and different countries will be at varying stages of progress.

While the individual and family focused psychological and clinical interventions described earlier can bring great benefits, such potential prevention or mitigation strategies, which impact of behaviours of concern and mental ill health, are rarely sufficient to ensure

an acceptable quality of life on their own. By prioritising the key areas listed below, countries can create a more inclusive and supportive environment for individuals with PWS and for those with other neurodevelopmental disabilities.

5.11.3 The mental and physical health of a child or adult with PWS and quality of social care and support to families are closely linked.

Meeting the behavioural and mental health needs of people with PWS is likely to require skills beyond that generally held by individuals' generic mental health services.

However, maintaining well-being, as well as the effectiveness of many interventions, depends on the presence of appropriate national policies and the existence of services, including:

- **Social policies and legislation:** Promoting social inclusion and ensuring access to education, employment, and other opportunities with the necessary support.

- **A skilled social care workforce:** Ensuring families, caregivers, and professionals are well-trained to support individuals with PWS effectively. (See additional guidance for professional caregivers here.)

- **Accessible and specialised health services:** Providing affordable and accurate early diagnosis when PWS is suspected, along with expert interdisciplinary care and treatment across an individual's lifespan, addressing both physical and mental health needs.

- **Respite and residential support:** Offering PWS-appropriate care options, which align with family wishes and cultural expectations, allowing families to also focus on other responsibilities and their own emotional needs.

- **Transition and crisis support:** Establishing systems to facilitate life transitions and provide timely interventions during crises.

- **A strong third sector:** The presence of organisations, such as National PWS Associations or other disability advocacy groups, that work to protect rights, provide resources, and support individuals with PWS and their families.

5.11.4 The extent and nature of the health needs of children and adults with PWS change during a child's development and over their life-time. Throughout life, health needs may be multiple, complex, and not necessarily treatable, although with the right knowledge and support, they can be managed.

Paediatric endocrinologists typically lead on the healthcare of infants and children with PWS, supported by dieticians and other health professionals as needed.

However, families of children with PWS report that obtaining guidance and treatment for behaviours of concern and mental ill health can be difficult, particularly so in adult life. Their child with PWS may be registered with the family doctor, who can provide general health care, but it is gaining access to specialist health care that is problematic.

If there is a national PWS Association, they are often a source of information. Where there isn't a National Association, IPWSO provides information in various languages (see translated guides here).

5.11.5 Recognising the challenge facing the families of people with rare disorders to obtain expert health care, the World Health Organization established an initiative on rare diseases. They proposed that all countries should have a rare diseases plan.

In addition, health-related Reference Centres for rare diseases should be identified. These Centres provide the necessary expertise and information with respect to each of the many rare diseases that have been identified.

Organisations such as Rare Diseases International (RDI), Eurordis, the National Organisation for Rare Diseases (NORD), the Asia Pacific Alliance of Rare Diseases Organisations (APARDO), Enfermedades Raras en el Caribe y América Latina (ERCAL), and other National and Regional third sector organisations support the implementation https://apps.who.int/gb/ebwha/pdf_files/EB156/B156_CONF2-en.pdf.

In recognition of the challenges facing people with rare diseases, in 2025, a resolution was passed by the World Health Assembly advocating for improvements in healthcare.

5.11.6 These initiatives primarily focus on the important issues of obtaining a diagnosis and accessing syndrome-specific treatments, but rarely focus specifically on the behavioural and mental health needs of people with neurodevelopmental conditions.

In countries such as France, networks like these for people with PWS are well established. In other high resource countries, there are a small number of multi-disciplinary specialist PWS clinics, where people with PWS can see a range of health specialists, ideally on the same day.

Such multidisciplinary clinics are popular among families, particularly early in life when diagnosis and information about PWS are so important.

5.11.7 The problem with such clinics, with respect to behaviours of concern and mental ill-health, is that families may live some distance away.

Under such circumstances, when the interventions recommended are not the prescribing of medication, but rather something more intensive, such as training support workers, and/or establishing a behaviour support plan, it is difficult for this to be delivered over a long distance. These are interventions that require time and local expertise. Technology may provide solutions to this.

In Australia telemedicine and telementoring programmes are used to provide guidance and support over large geographic areas (see Ashley et al., 2023 for experience during the covid pandemic).

Project ECHO established by the University of New Mexico, USA, is another example where technology is used to upskill those working in remote areas.

5.11.8 In Norway, the organisation at Frambu (www.integratedcareorganisation.org) is an established national resource where people with specific conditions and their families can attend for residential courses on specific rare conditions.

In the UK the National Health Service (NHS) supports Child Development Centres where young children with developmental disabilities are seen. There are also Social Service and NHS district-based specialist multidisciplinary teams for children and adults with intellectual (learning) disabilities.

These teams include behaviour specialists, specialist nurses, speech and language therapists, clinical psychologists, and psychiatrists. Those in these disciplines should have the skills to address the behavioural and mental health needs of people with PWS.

5.11.9 Each of these service models meeting the behavioural and mental health needs of people with PWS have their strengths and weaknesses. A general concern, regardless of the service model present in a country, is that specialist with an interest in, or the experience of, the needs of people with complex neurodevelopmental disabilities, including those of children and adults with PWS are not available.

One major recommendation is that these disabilities and the services required are given a much higher profile, so that the services to meet these specific needs of children and adults with neurodevelopmental disabilities can be recognised and specifically planned for.

5.11.10 Achieving the above goals requires knowledge, political commitment, and adequate resources. For countries where resources are severely limited, advocating for these services presents a significant challenge.

IPWSO, National PWS Associations, and regional and national rare disease groups can serve as powerful advocates. In some regions, rare disease alliances are leading the efforts, for example, in Ghana, Kenya, and South Africa.

In other countries, National PWS Associations are at the forefront, as seen in Malaysia and Australia. Romania is an example of a country where advocacy efforts are driven by a combination of rare disease organisations working together.

5.11.11 For people with PWS who live in countries that have the necessary resources and a well-established healthcare system the profile of need may well change as, hopefully, new and effective treatments for hyperphagia and some of the behaviours of concern become available. In addition, globally, not only are there differences in terms of health and social care resources, and knowledge about PWS varies markedly.

We have heard how services if available at all, may be limited to, and accessible only to those living in urban areas, sometimes just to the capital of a country. Given these marked differences, there is no one answer or one design for services to meet the complex needs that are the focus of this report.

In addition to the genetic and the general medical expertise needed, there has to be the necessary skills available to support families and people with PWS to manage, and where possible, treat behaviours of concern and mental-ill health. Some of this expertise may well be located in regional multidisciplinary clinics, but there also needs to be local expertise that can provide support to families.

5.11.12 Respite care for families and supported living or residential support in adult life for people with PWS is also an essential part of the mix of services needed.

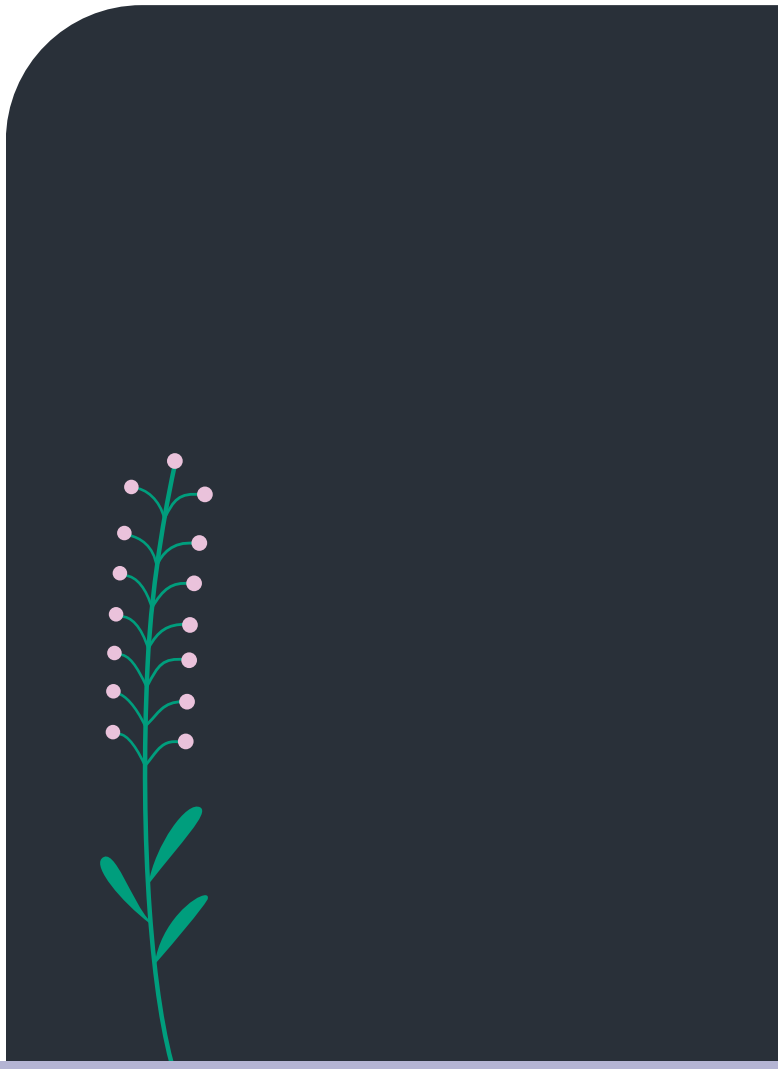
In some countries there are group homes that provide specifically for adults with PWS, where food security and management of the food environment is an integral part of support (see Hughes et al., 2024, for an evaluation of these services).

The needs are not simply those related to hyperphagia but also include the management of other behaviours and addressing those needs that arise because of the presence of intellectual, cognitive, social, and functional impairments.

5.11.13 Part 5 ends with an account given by a person with PWS and their family that describes the transition from school to adult life as an example of how understanding of the impairments and needs of a person with PWS can inform support.

It illustrates the delicate balance between meeting the specific needs of a person with PWS to ensure their on-going physical and mental health and their wish to be more independent.

It also demonstrates what can be achieved if families feel supported, if all concerned understand the specific needs of people with PWS, and if the necessary health and social services are in place and staff in these services are willing to learn about the unique needs of people with this syndrome.



PERSONAL ACCOUNT ON TRANSITION FROM SCHOOL TO ADULT LIFE

John was diagnosed as having PWS very early in his life. During his childhood he had been helped by his parents to better understand what it means to have PWS. John described that there were times when he got very angry and when he had been upset with his parents about the limitations around food and access to money.

Transitioning from school was challenging for John. He had had a supportive and structured learning environment at school and his needs were well understood by his teachers. He prepared on many levels for the move to share a house with three other young people, two of whom he knew, all of whom had PWS. His social worker helped him apply for a place at a Further Education College, where he hoped to develop his independence skills. Staff from the new house met with John and his parents, and John understood that staff were there to help him. He felt comfortable that they understood his needs. As well as attending College he wouldhave work experience with a local company who have supported people with PWS in the past.

John worries that he can get angry and upset at times. He was encouraged to talk to the support staff before he moved to the house so that they could help him when he begins to feel upset. He appreciates that the move away from his parents would not be easy, but he understands that his parents will visit him and that he could spend time at home, particularly when his sister and brother were there. He has registered with the local doctor, who will prescribe his regular growth hormone treatment. His future support staff have advised him that they spoke to the local specialist health services about receiving additional help for his behaviour, if that is needed. His parents supported him documenting these plans in his Life-Story book so he can remind himself when he needs to about what will be happening. Now, John is transitioning well to his new home. He has experienced some stress and occasional outbursts, but he has started College and leads a full life.

Account from family in the UK

Transition to adult life is not easy as this is a time of change and uncertainty. For some people with PWS and their families, even though the process is well planned, it can be particularly challenging, and for others it may be relatively uneventful. However, the above case history illustrates some general principles that underpin good care, particularly at times of transition. These may not eliminate challenges, but they may make change and make the transition more manageable (Poitou et al., 2023).

As the individual strengths and challenges a child with PWS experiences become apparent, be open about the implications of having PWS. Clarify that it is no one's fault, but that it does necessitate support in certain areas of their lives, such as managing access to food.

It may be helpful for the person to have regular interactions with other people with PWS so they can learn from an early age how they live, and so each person with PWS can play a meaningful role in identifying solutions that may be helpful for them. If the person with PWS is entering a service where there are other people with PWS, it may be helpful for them to meet in advance so they can ask questions and learn about daily routines.

Whenever possible, when change is anticipated, plan ahead, reduce uncertainty, and record key information for easy reference by everyone involved, including the person with PWS.

Although transitions may occur at short notice due to emergencies, ideally, significant transitions should be planned over a long period. It is important to allow adequate time for the person with PWS to build a relationship with the people who will be supporting them, and to ensure that all the relevant information needed is conveyed and understood by the new staff.

It is likely that the person with PWS will find it helpful to become familiar in advance with the new location. Before the move staff may find it useful to visit the person with PWS in their home to better understand their existing living arrangements and routines. It may take many months for all the elements of a transition to a new home and service to be completed (e.g. visits, information preparation, finding a new GP or other medical services, and arranging educational services or work).

Just as the pace of the transition should be determined by the needs of the person with PWS, so should the pace of their integration into new activities in their new setting. Some people with PWS may be able to enter a residential setting, begin a new programme of education and/or work experience, and engage with new medical providers within a short time frame. Others may benefit from phasing in new activities over a much longer period.

Special consideration should be given to preparing the person with PWS for the food arrangements in their new setting. This may involve them meeting in advance with a dietician or other person who has oversight of nutrition in their new service to discuss their likes and dislikes. It may involve them receiving a meal plan before moving to the new setting or being given information about when they will find out about meal plans. The person with PWS may need ongoing reassurance about the times of meals and other food security arrangements.

Many people with PWS receive ongoing support from a range of medical professionals (e.g. endocrinologist, respiratory consultant, orthopaedic consultant, psychiatrist). The transition plan will need to clarify if the person will continue to see the same medical professionals or if it will be necessary to identify similar services in the new location.

With the history of a person with PWS in mind, in transition, plan with those who will be providing support in the future how potential challenges will be met, identify if there are services locally that are available to provide support if needed or in a crisis, have a structured plan for continuing family contact and for visits home, and how communication with the family will occur.

Part 6: Significant open questions and future research and development needs

Introduction

6.0.0 Global challenges and opportunities in mental health and quality of life for people with PWS

6.0.1 This Report presents the collective perspective of members of the IPWSO Mental Health Network (IMHN), an international multidisciplinary group of health and social care professionals and parents of children with PWS. The primary emphasis of the Report is on well-being, quality of life, and the mental health of people with PWS and their families.

In this final part of the Report we reflect on gaps in our knowledge and have proposed what we have referred to as a 'mental health research and development road map'.

This road map has three components:

- The first is concerned with global issues and how we might better appreciate and understand the global differences that exist.
- The second relates to well-being and quality of life and the focus is on policy and clinical and social care practice and service development.
- The third is the need for more fundamental research into PWS so new specific treatments can be developed.

6.0.2 For those living in higher resource countries with established health care systems these are optimistic times, particularly given the recent USA approval in spring 2025 of the first medication to treat hyperphagia in children and adults with PWS. However, in the USA, the cost of this new medication is substantial.

With other trials ongoing or planned, not only for hyperphagia but also for other behaviours and for excessive daytime sleepiness (in this case an existing medication, pitolisant), there is the real possibility of transformative treatments for hyperphagia and for other aspects of the neuropsychiatric phenotype of PWS.

However, for families in many parts of the world, their struggle is to get a diagnosis to account for their child's disability, to gain access to clinical expertise and knowledge, and to have the benefits that come with support from other families. In IPWSO we are increasingly aware that such inequalities may increase if new effective treatments are only available in a few countries.

6.0.3 Early in the discussions of the IMHN, we agreed on the need to go beyond a narrow understanding of mental health to include consideration of concepts such as well-being and quality of life.

We have argued in the Report that promoting and maintaining well-being and the quality of life of people with intellectual disabilities and/or neurodevelopmental conditions, for instance PWS, requires government policies that foster social inclusion, services that provide appropriate support, an early and accurate genetic diagnosis, and timely access to specialist health expertise and professional support when needed.

However, we have very limited information globally as to the specific barriers in different countries that prevent someone with PWS and their family receiving the level of care needed and therefore what needs to be done to improve outcomes.

6.0.4 In the Report we have also set out our understanding of what we have referred to as 'dimensions of mental ill health' that commonly impact the lives of children and adults with PWS and their families.

Drawing on the experiences of people with PWS, families of children with PWS, the theoretical perspectives of different health disciplines, and the expertise of professional social care providers, we have described how behaviours of concern and mental ill health present and their likely causation and the existing treatments.

But even in high resource countries, we hear from families that access to expertise to advise on the prevention and treatment of these challenges is variable and in many countries this expertise is limited or absent.

6.0.4 We have also highlighted the importance of support for families, access for people with PWS to essential services beyond those provided by health, such as education and employment, and the importance of having access to knowledge and an understanding of PWS.

Questions arise as to what is needed at national and local levels to promote well-being and quality of life for people with PWS, what additional services are required to meet the specific behavioural and mental health needs, what the design of these services looks like, and what skills are required?

Cultural diversity and economic divergence

6.1.0 Economic and cultural divergence

6.1.1 The health disparities observed between countries created a challenge for the Mental Health Network in formulating recommendations and highlighted significant gaps in our knowledge. The topics of research in this field remain heavily determined by those working in high-resource countries with Western political systems, scientific frameworks and perspectives.

At IPWSO, families worldwide have shared their struggles with the behavioural and mental health challenges of their child with PWS. However, we do not have findings from any systematic studies of the exact nature and extent of global inequalities experienced by people with PWS and their families.

6.1.2 We acknowledge that countries differ significantly in their economic status and in the resources and expertise available to them to address the mental health and social care needs of people with complex neurodevelopmental conditions. This also includes the possibility of cultural differences in how the needs of people with PWS are understood.

We have limited information about services and what is available to people with PWS and their families, particularly with respect to quality of life, behaviour and mental health. Perceptions of family responsibility and beliefs about behaviours and mental ill health associated with PWS can vary.

We know of no studies that have investigated how the impairments and behaviours associated with having PWS are conceptualised and understood in different countries and cultures and how this understanding in turn might impact on the lives of people with PWS and their families.

6.1.3 A recent survey undertaken by IPWSO has found that globally, access to growth hormone remains challenging. This is a treatment with proven benefits that was approved in Europe and North America over 20 years ago.

In any treatment development pathway, the challenge is to ensure that treatments shown to be effective are approved, available, and affordable to people with PWS. Experience with growth hormone suggests new treatments might not be accessible to most people with PWS.

We need to better understand how access to new treatments for hyperphagia, other behaviours of concern, and for mental ill health can be achieved and to find ways of overcoming barriers to treatment access and affordability.

6.1.4 Even in high resource countries with established healthcare systems it became clear that a fundamental challenge is ensuring that people with PWS and their families have access to the necessary expertise with respect to the prevention and treatment of behaviours of concern and mental ill health.

We consider that it is in this space that National PWS Associations, IPWSO, and FPWR have crucially important roles to play as sources of reliable research informed guidance, as advocates for good practice, in supporting and encouraging research, disseminating findings, and helping families to gain access to support and treatment when required.

However, the need likely extends beyond health services and treatment to include tackling issues such as stigma, access to education, employment and support services, financial assistance for families, and availability of services staffed by appropriately skilled professionals.

6.1.5 These above challenges are common to all individuals living with rare disorders. How can the necessary expertise be provided under the very different conditions across the world where people with PWS and their families live and with very different levels of resources?

The World Health Organization has an active programme exploring how technologies can be used to facilitate access to expertise and treatment to remote parts of the world or where expertise is not available. Can telehealth or tele mentoring be helpful?

6.2.0 Generational change, the family, and new ideas

6.2.1 The PWS neuropsychiatric phenotype has been documented in numerous studies extending back over many years. However, it remains unclear whether these earlier findings on the nature and severity of the behavioural and psychiatric phenotype will be found to the same extent in a younger generation of people with PWS as they age.

Younger individuals from well-resourced countries often receive early diagnoses, live in environments that control food intake to prevent obesity, and receive growth hormone treatment and sex hormone replacement therapy from a young age.

If early access to appropriate care influences subsequent developmental trajectories and rates of behaviours of concern, significant improvements should be observed in regions where early diagnosis and specialised care have been available for some years. Whether this is the case or not has not been systematically investigated.

6.2.2 Establishing food security and a healthy lifestyle from early in life to prevent obesity developing has been seen as best practice in general.

The benefits to the person with PWS having an appropriate structure around the food environment and physical activity are apparent and extends beyond just preventing severe obesity and its complications to also reducing behaviours of concern and, importantly, enhancing overall well-being and quality of life.

6.2.3 Such an approach to the prevention of obesity, which is seen by some as overly rigid, is being questioned, particularly with respect to the younger generation of people with PWS.

In countries with well-established health services, children with PWS, who have been diagnosed early in life, have in general had a better start to life than previous generations. After the initial need for augmented feeding following birth, the suggestion is that children, adolescents, and adults with PWS should then be more involved in the design and handling of food. It is argued that the earlier they are involved and they have some responsibility for food and nutrition, the greater the likelihood that they will be able to learn to regulate their own diet and weight management as adolescents and adults, at least to some extent.

This less restrictive perspective may be increasingly relevant with the advent of treatments for hyperphagia. These new medications may not by themselves completely prevent hyperphagia, but they may allow the person with PWS themselves to exert appropriate limits on their eating behaviour, particularly if they are aware of the issues and are well supported.

6.2.4 It is important to note that at present there is no published research that has systematically explored the extent to which this younger generation of people with PWS, who may be more aware of the impact of PWS, can manage their own diet. There is also a very limited understanding as to the barriers and facilitators to the implementation of family and social care practices around mealtimes, how effectively this combination of managing access to food and ensuring food security can be maintained over time by those providing support, and the extent to which such support can be modified over time.

While food is often central to a country's culture, it is unclear if mealtime traditions influence attitudes towards managing food access and how any resulting tensions are resolved.

Furthermore, people with PWS also have their individual profiles of need and how well they might succeed in managing their own food environment will also depend on this, and how the daily structure of their life is organised and the extent of the opportunities available to them.

6.2.5 In the case of emotional outbursts, psychological and environmental strategies can reduce the severity and frequency of outbursts. However, there is also developing evidence that autonomic nervous system dysfunction is the biological underpinning for this increased risk of these behaviours in people with PWS.

These two examples, hyperphagia and emotional outbursts, illustrate this environmental-biological dynamic that we have argued is central to understanding behaviours of concern. Better understanding this dynamic will inform treatment development and importantly help in the evaluation of risk.

6.2.6 We have emphasised throughout the Report the importance of, and impact on, the family when one of their children has PWS. This extends beyond the parents to include the siblings and other generations of family members.

In a recent publication (Micallef Pulè & Hughes, 2025) the nature and extent of this has been reported in a study involving 135 parents and 45 siblings from 31 countries.

High rates of anxiety, depression and PTSD were observed, with, for example, 67% of parents reporting abnormal levels of anxiety. The impact on the family correlated with levels of food problems and emotional outburst affecting the family member with PWS. Importantly, they showed that family cohesion was an important mitigating factor, providing some protection for the family from these adverse effects. The authors point out that such effects in turn impact on the ability of the family to provide support to their child with PWS.

Families are crucial in trying to bring together what are often the offers of limited and fragmented interventions provided by poorly coordinated services. We need to better understand how the 'therapeutic resource' that is the family, can be supported to maintain family cohesion and by access to techniques, such as mindfulness, that can increase resilience of mothers of children with neurodevelopmental disabilities (Dykens et al., 2014).

Applying knowledge

6.3.0 Four principles from basic, social, and clinical sciences

6.3.1 It was agreed that PWS is fundamentally a condition whose core manifestations are a consequence of atypical brain development. The PWS-specific dimensions of mental ill health, as outlined in this Report, are best understood as resulting from underlying biological vulnerabilities.

Some of these vulnerabilities stem from impaired hypothalamic development, others from disruptions in emotion and mood regulation, and some are more directly related to the effects of cognitive impairment. These biologically based vulnerabilities interact with past and present environmental influences, which, to varying degrees, influence the development and persistence of certain behaviours or abnormal mental states over time.

6.3.2 Since the 1990s, the genetic basis of PWS has been well established and genetic testing progressively refined for diagnostic purposes. However, the pathways linking the absence of expression of specific maternally imprinted gene(s) located at 15q11.13 to atypical brain development and impaired neural function, to the emergence of the neuropsychiatric phenotype, remains poorly understood and defined.

Genetically modified animal models of PWS, pluripotent stem cell technologies, and the application of advanced neuroimaging and other neuroscience techniques provide the means for studying such pathways at molecular, cellular, and neural levels. The goal is to trace how the lack of expression of certain maternally imprinted genes at 15q11-13 leads to abnormal brain development, which then results in hyperphagia and the physical and neuropsychiatric traits of PWS.

6.3.3 Psychologically informed approaches for early intervention have been evaluated in children with neurodevelopmental conditions with the aim of improving subsequent developmental trajectories. Trials of intranasal oxytocin given in early childhood with the aim of improving social cognition and social functioning are also underway.

Whether it is the use of established psychological and educational interventions early in life or the giving of a particular treatment, such as oxytocin, it is essential that the critical period in development when such treatments have the greatest chance of being beneficial for children with PWS is identified.

6.3.4 Clinical trials in PWS are increasingly common. However, whether for hyperphagia or for other behaviours what has not been extensively investigated is whether there are biomarkers that might correlate with outcome measures and potentially could be used to predict the likely efficacy of a new treatment.

For treatments of hyperphagia such biomarkers might include changes in hormone levels, such as those of ghrelin or leptin, measures of autonomic nervous system function; or evidence of changes in patterns of neural functioning and connectivity, differences in neural activation thresholds, or changing neurochemical spectra as measured using different forms of neuroimaging.

Such an approach has the potential to provide important additional evidence that could be put to regulators when they are asked to approve new treatments.

6.4.0 The complexity of interventions: Pharmacological and non-pharmacological

6.4.1 It is often stated that growth hormone is the only approved clinical treatment for people with PWS.

While this is true in a narrow sense, treatment in its broadest sense extends far beyond medication. It includes, for example, the application of psychological theory and psychologically informed interventions to improve functional skills and modify challenging behaviours, support strategies that reduce uncertainty and feelings of anxiousness, and the effective management of the food environment.

In addition, especially when considering well-being and quality of life the interventions may be at societal level, such as having access to financial benefits or the presence of support to enable attendance at school, or access to supported employment.

The translation pathway under these circumstances is about the translation of knowledge into practice and/or into cultural, societal or political change.

We need to understand both the potential barriers and the enabling factors that influence the translation of knowledge into changes in policy and practice.

6.4.2 For the trial of potential new medications, pharmaceutical companies raise financial support through established commercial arrangements to fund the clinical trials. However, such arrangements only work with respect to treatments that will bring a financial return for the company concerned.

There is also the need to evaluate treatments where such funding models do not apply. This may involve psychological treatments, psychiatric medications for people with PWS, or examining the link between available support and mental and physical health.

This is not to be critical of such commercial models; they are very likely to deliver new treatments, rather it is to highlight that other modalities of treatment should not be forgotten.

Even if there is a treatment for hyperphagia, good and informed support will still be required. Having evidence to make the case for support or for access to some form of effective psychological intervention will be required so that it is available and funded.

6.4.3 As covered in the Report, clinical trials indicate that hyperphagia may respond to pharmacological interventions. When this Report was first being drafted, no treatments had been approved for treating hyperphagia. This has now changed with VYKAT XR being approved in March 2025 by the U.S. Food and Drug Administration (FDA).

This is a milestone to be celebrated, first because it provides hope to people with PWS and their families that a new treatment is available which, to some degree and in some people, reduces the drive to eat. As with many medications there are side effects, and especially in the case of VYKAT XR a close control of blood sugar is needed.

Secondly, it shows that hyperphagia is not something that is fixed and untreatable, hopefully leading to the development of further treatments.

Thirdly, when a medication with a known mode of action demonstrates potential efficacy, it provides insight into the underlying mechanisms that drive hyperphagia. This understanding could subsequently inform the development of further treatments.

However, there has been limited research that has attempted to map observed responses or non-responses to specific potential treatments for hyperphagia to measures of activation or connectivity of the feeding and reward pathways in the brain. Such research would inform the selection of future treatments and importantly help establish whether hyperphagia in PWS is a consequence of a defect in a specific feeding pathway.

6.4.4 Among the global PWS community there is understandably excitement about the potential of new treatments. However, it is also important to express some caution.

In the case of treatments for hyperphagia, once they have been shown to be efficacious through the use of outcome measures such as the Hyperphagia Questionnaire for Clinical Trials (HQCT), and the treatment has been approved there are further questions that need to be answered.

To be able to make the case for funding for such treatment it is important to show that these treatments are also effective in the real world and that benefit outweighs any risks. This would require showing that people with PWS had more control of their eating behaviours and had greater freedoms without fear of severe obesity developing.

Are such treatments cost effective in terms of reducing the risk of obesity related illnesses and/or reducing the need for high levels of support?

Do such treatments have benefits that extend beyond reducing hyperphagia and do the improvements observed make a real and measurable difference to quality of life?

Where a case can be made for a treatment's approval, affordability is likely to be a further challenge and novel manufacturing and funding arrangements are likely to be required for those with PWS living in medium or low resource countries.

6.4.5 During the course of the preparation of this Report it became clear that there were differences and at times disagreements about how emotional outbursts should be best understood and treated.

There was evidence that certain pharmacological agents might be of some value, and there was a strong view that more psychologically and behaviourally orientated approaches were the answer.

Are emotional outbursts a result of specific cognitive impairments affecting management in a demanding world, or do they stem from impaired emotional control? The answer to such questions would change the approach to intervention.

6.4.6 Detailed research has identified the common triggers and patterns for emotional outbursts, and there are established methods for reducing their frequency and more effectively managing them. However, the nature, extent, and pathophysiology of any biological vulnerability to such outbursts is uncertain.

Interestingly, outbursts may respond to manipulation of the autonomic nervous system through stimulation of the vagus nerve.

While these findings are preliminary, they again highlight how trials and proof of concept studies can inform our understanding of possible causal mechanisms that may be modifiable.

A large trial of transcutaneous vagus nerve stimulation is presently being undertaken in the USA by FPWR.

6.4.7 Another issue identified concerns the various atypical mental states associated with PWS. How are these best described and understood?

In the Report we moved away from terms like 'anxiety' or 'anxiety disorder', opting instead for 'anxiousness' to refer to a commonly observed mental state in people with PWS.

In addition to anxiousness, affective instability, affective disorders, and affective psychotic illness were also recognised as prevalent, with the last of these being more common in people with PWS due to chromosome 15 mUPD.

At present the best approach to treatment for these abnormal mental states remains unclear, as the underlying pathophysiology is unknown.

We have proposed that using adapted systems of clinical classification, such as Research Domain Criteria, may be one approach to advancing understanding.

The fundamental question is whether phenomena like anxiousness, affective abnormalities, or psychotic illness in people with PWS share similar pathophysiology with these states in typically developing individuals. If not, in what way are they different?

6.4.8 With respect to the psychotic illness observed in people with PWS, the fact that it occurs significantly more commonly in those with the mUPD suggests that it is not just having PWS that predisposes, but the additional genetic difference that exist when having a chromosome 15 maternal disomy.

For example, levels of expression of maternally expressed paternally imprinted genes on chromosome 15 are elevated in those with mUPD in comparison with chromosome 15 deletion.

At present psychopharmacological treatments for psychosis in people with PWS have been based on experience and research from treating psychotic illness in the typically developing population.

However, if brain differences were to be identified between the main genetic sub-types, that would provide an explanation for the differential risk of psychosis this might help guide future psychopharmacological treatment selection.

A road map for PWS mental health research and development

6.5.0 The need for a road map

6.5.1 In this section, we set out a series of questions and propose a 'PWS Mental Health Research and Development Roadmap'.

The road map takes a global perspective highlighting the importance of policy and service developments aimed at optimising well-being and quality of life.

We also include research and clinical trials that lead to the development and evaluation of new treatments and interventions for mental ill health and behaviours of concern.

6.5.2 This road map complements others, such as those prepared by FPWR USA and the Prader-Willi Research Foundation of Australia (PWRFA).

It differs in emphasis in that the IPWSO road map is specifically concerned with the following:

- Global health inequalities affecting people with PWS
- Well-being and quality of life
- Dimensions of mental ill health including behaviours of concern

6.5.3 Research focusing on the mental health and behavioural needs of people with PWS is particularly challenging.

As this Report has outlined, factors at societal, family, and individual levels have an impact on the well-being, quality of life, and mental health of people with PWS and their families.

Also, PWS is a condition where it is the absence of expression of specific maternally imprinted gene(s) that influence subsequent brain development in ways that are specific to PWS. This results in a characteristic physical and behavioural phenotype.

For these reasons the expertise and methodologies of disciplines as diverse as the social sciences and neuroscience are required to establish the necessary evidence base.

6.6.0 Priorities for mental health research and development

6.6.1 For well-being, quality of life and mental health, fundamental questions include identifying risk and protective factors for people with PWS at the following levels:

- Societal
- Community
- Family
- Individual

6.6.2 For dimensions of mental ill health, including behaviours of concern, key questions involve identifying the neural mechanisms, pathways, and environmental risk factors, as well as how these interact. Answering these questions would inform the development of effective treatments and interventions for the following issues:

- Hyperphagia
- Emotional outbursts
- Rigidity and repetitive behaviours
- Anxiousness
- Affective disorders
- Psychotic illness

6.6.3 At a global level we need to improve our understanding of the reasons for differences in the care and treatment of people with PWS and the impact of cultural and national factors on the diagnosis, management and treatment of behaviours of concern and mental ill health. These include:

- Stigma and its impact on how people with PWS are perceived
- Government policies, and societal attitudes
- Cultural differences and views on support practices and interventions
- Health and social care infrastructure

6.6.4 We need to develop an understanding of what good support would look like and how it might adapt to differences between countries, such as urban versus rural settings. Where populations are sparse and/or expertise is limited how might technologies such as telehealth and telementoring be used? Could wearable and other technologies be used for monitoring physical and mental health? The types of support include:

- Family support
- Early intervention
- Direct support for people with PWS
- Access to health care for behaviours of concern and mental ill health
- Crisis management

6.7.0 Conclusion

6.7.1 We conclude by returning to this contrast between the opportunities of new treatments that are and will be available to some, which have the potential to transform lives, on the one hand, and on the other, the observation that in many parts of the world the challenge faced by families of children with PWS is to receive a diagnosis, have access to information, and for their child to have good health care. To truly improve the mental health and well-being of people with PWS we need to think beyond treatments to society itself and access to opportunities and to social inclusion. The IPWSO Mental Health Research and Development Road Map (**Figure 20**) seeks to illustrate this.

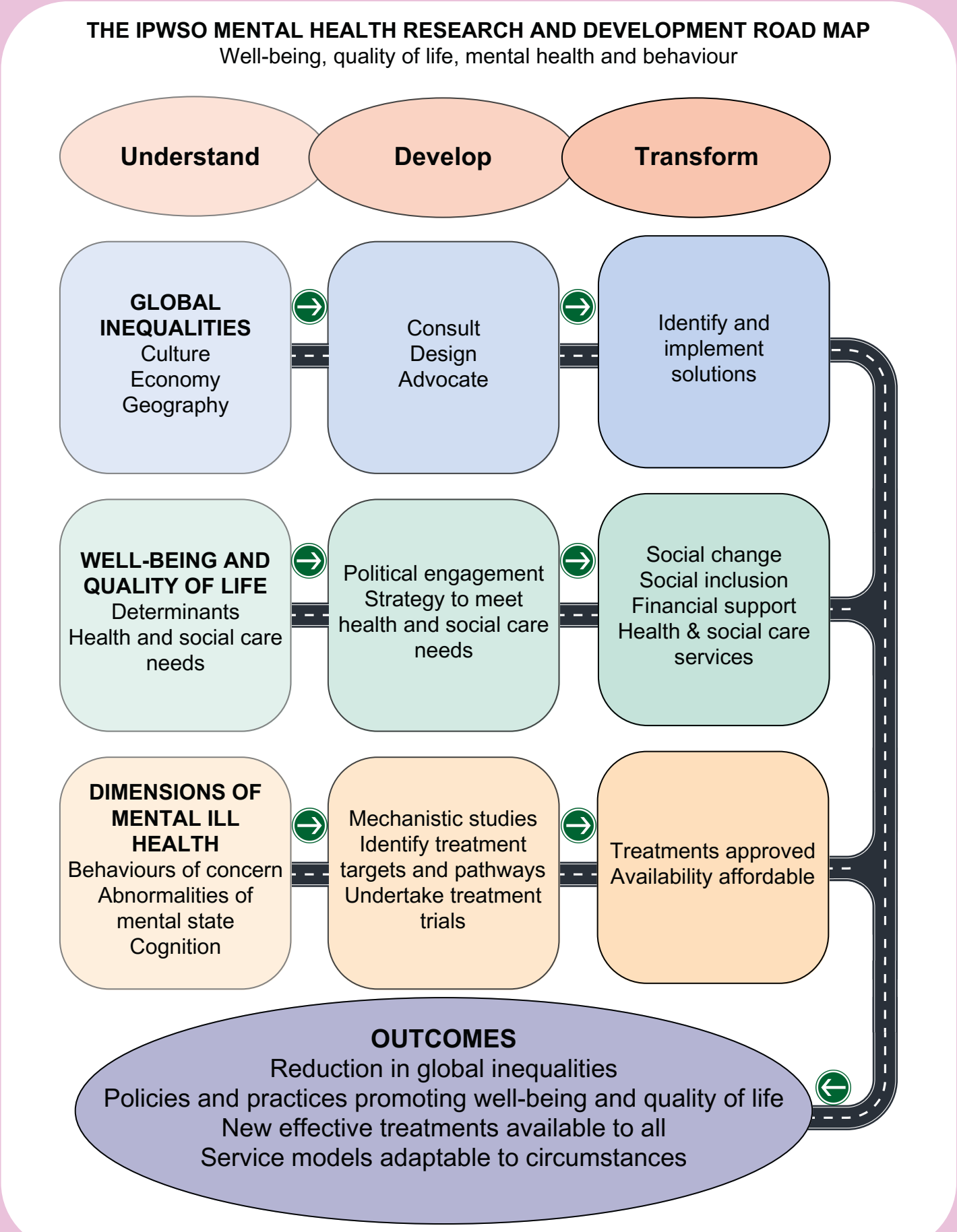


Figure 20 The IPWSO Mental Health Research and Development Road Map

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Vision

A world where people with PWS and their families receive the services and support they need to fulfil their potential and achieve their goals.

Mission

To unite the global PWS community to collectively find solutions to the challenges of the syndrome and to support and advocate for people with PWS and their families, PWS associations, and professionals who work with people with PWS.

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