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REVIEW ARTICLE

Requirements for improving health and well-being of children with Prader-Willi syndrome and their families

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Abstract: Prader-Willi syndrome (PWS) is a rare genetic condition with multi-system involvement. The literature was reviewed to describe neurodevelopment and the behavioural phenotype, endocrine and metabolic disorders and respiratory and sleep functioning. Implications for child and family quality of life were explored. Challenging behaviours contribute to poorer well-being and quality of life for both the child and caregiver. Recent evidence indicates healthy outcomes of weight and height can be achieved with growth hormone therapy and dietary restriction and should be the current target for all individuals with PWS. Gaps in the literature included therapies to manage challenging behaviours, as well as understanding the effects of growth hormone on respiratory and sleep function. New knowledge regarding the transition of children and families from schooling and paediatric health services to employment, accommodation and adult health services is also needed. Developing a national population-based registry could address these knowledge gaps and inform advocacy for support services that improve the well-being of individuals with PWS and their families.

Key words: endocrine; hyperphagia; Prader-Willi syndrome; quality of life; sleep disordered breathing.

Key Points

1 Food-seeking activities, restrictive or repetitive behaviours and difficulties with social communication and reciprocity in individuals with Prader-Willi Syndrome have significant consequences for maternal and family well-being.
2 Growth hormone therapy has contributed to reduced obesity, but the optimal initiation, dosage and continuation of the therapy and its effect on respiratory and sleep regulation and function remains unclear.
3 Evidence for supportive therapies in Prader-Willi Syndrome is poor; development of evidence-based management and advocacy for affected families require a more comprehensive analysis of relevant covariates influencing quality of life in a large, population-based cohort.

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Prader-Willi syndrome (PWS) is a rare disorder affecting approximately 1 in 15 000 live births[1,2] and results from a lack of expression of paternal genes in the 15q11-q13 region on chromosome 15. Overall life expectancy is shortened such that 13–20% of people with PWS have died by 35 years in previously published cohorts.[3,4] Recent improvement in survival is attributed to earlier diagnosis and greater therapeutic intervention in delaying or preventing the onset of obesity.[5]

There are many challenges for affected children and their families. Appetite dysregulation, most notably hyperphagia, and the difficult behaviours exhibited by individuals with PWS necessitate high levels of supervision, environmental management and behavioural interventions from caregivers each day. Ongoing vigilance and management can lead to higher levels of distress and reduced quality of life for caregivers of individuals with PWS compared to caregivers of individuals with other chronic congenital conditions or the general population.[6–8] This review will describe PWS, focusing on appetite dysregulation, respiratory function and sleep disordered breathing and challenging behaviours, and will explore their implications for child and family well-being and quality of life.

Methods

A review of the literature describing the health and well-being of individuals with PWS and their families was performed. The inclusion of family well-being was strongly endorsed as a component in our study by our Western Australian PWS Consumer Reference Group. Article titles and abstracts were searched in the following databases: Medline, PubMed, CINAHL and Google Scholar for PWS using variations of the following key terms: health, well-being, quality of life, life satisfaction, stress, coping, managing, meaningful, impact, psychosocial, values, burden, family functioning, family cohesion, support, response, strain, education, affective disorders, anxiety, depression and psychology. The references of relevant articles were also examined for inclusion in the review. Non-English articles were excluded.

Table 1 Clinical indications for diagnostic testing of Prader-Willi syndrome (adapted from Gunay-Aygun *et al*.,[11] Cataletto *et al*.[63] and Angulo *et al*.[12])

Age at assessment	Clinical features prompting DNA testing
Birth to 2 years	Hypotonia with poor suck
	Reduced fetal movement
	Cryptorchidism
2–6 years	Hypotonia with a history of poor suck
	Global developmental delay
	Short stature and/or growth failure associated with accelerated weight gain
	Hypogenitalism/Hypogonadism
6–12 years	Hypotonia
	Global developmental delay
	Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled
	Short stature and/or decreased growth velocity
13 years to adulthood	Cognitive impairment, usually mild intellectual disability
	Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled
	Hypogonadism and/or typical behaviour problems (including temper tantrums and obsessive–compulsive features)
	Short stature and/or decreased growth velocity

Results

Genetic cause

PWS was initially described by Prader *et al*. in 1956,[9] with the diagnostic criteria revised by consensus in 1993[10] and revised again in 2001 to inform clinical indications for genetic testing (Table 1).[2,11] PWS results from the absence of functioning paternal genes on chromosome 15 in the 15q11-q13 region.[2] The roles of these genes are not completely understood, but they are known to contribute to neural development and function,[12] with their absence affecting multiple systems across the life-span (Fig. 1). Approximately 60–70% of all PWS cases result from *de novo* deletions on the paternally inherited chromosome 15 within this region, and a further 25–30% of PWS cases are associated with maternal uniparental disomy of chromosome 15.[2] The remainder are associated with erroneous silencing and disrupting of the function of the paternally inherited genes in the q11-q13 region following defects, translocations or inversions in the imprinting centre located on the paternal chromosome 15.[2]

Neurodevelopmental phenotype and challenging behaviours

Neonates with PWS may exhibit severe hypotonia, feeding difficulties resulting in the need for assisted feeding and failure to thrive.[9,11] Other features seen during infancy include hypogonadism, mild craniofacial abnormalities such as a narrow bi-frontal diameter and almond shaped eyes and global developmental delay.[2] Delayed motor development is observed in most (90–100%) children with PWS.[2,13] Developmental milestones such as sitting and walking are usually achieved at approximately double the age of typically developing children.[2,13] There are limited musculoskeletal data on strength and fitness, but some evidence indicates that physical activity programmes for primary school-aged children with PWS can increase daily physical activity.[14] From 2 or 3 years of age, height velocity usually slows, and there can be excessive weight gain without strict dietary regulation.[2] Children become increasingly obsessed with food, and the majority develop the hallmark characteristic of hyperphagia with loss of satiety.[2]

Variable cognitive impairment affects most individuals with PWS, presenting as mild-to-moderate intellectual disability and delays in language development,[2,15] particularly expressive language.[16] However, intellectual functioning is classified as borderline normal in some individuals.[2,15] Difficulties with social communication and reciprocity from early childhood are commonly reported for individuals with PWS,[17,18] with difficulties in establishing social relationships also described in the literature.[15–17]

The behavioural profile of PWS also includes restricted or repetitive behaviours.[17,18] Combined with difficulties in social functioning, these behaviours are sufficient for a concurrent diagnosis of autism spectrum disorder in approximately a quarter (26.5%, $n = 786$) of individuals with PWS.[18] Other problematic behaviours include emotional lability and temper tantrums, especially in response to interruption of food-seeking and repetitive behaviours; impediments to desired goals; changes to routines; or being presented with conflicting information, particularly pertaining to unjust deviation from social expectations. Comorbid psychiatric disorders can be common, for example, oppositional defiant disorder was diagnosed in 20% of 8- to 14-year-old

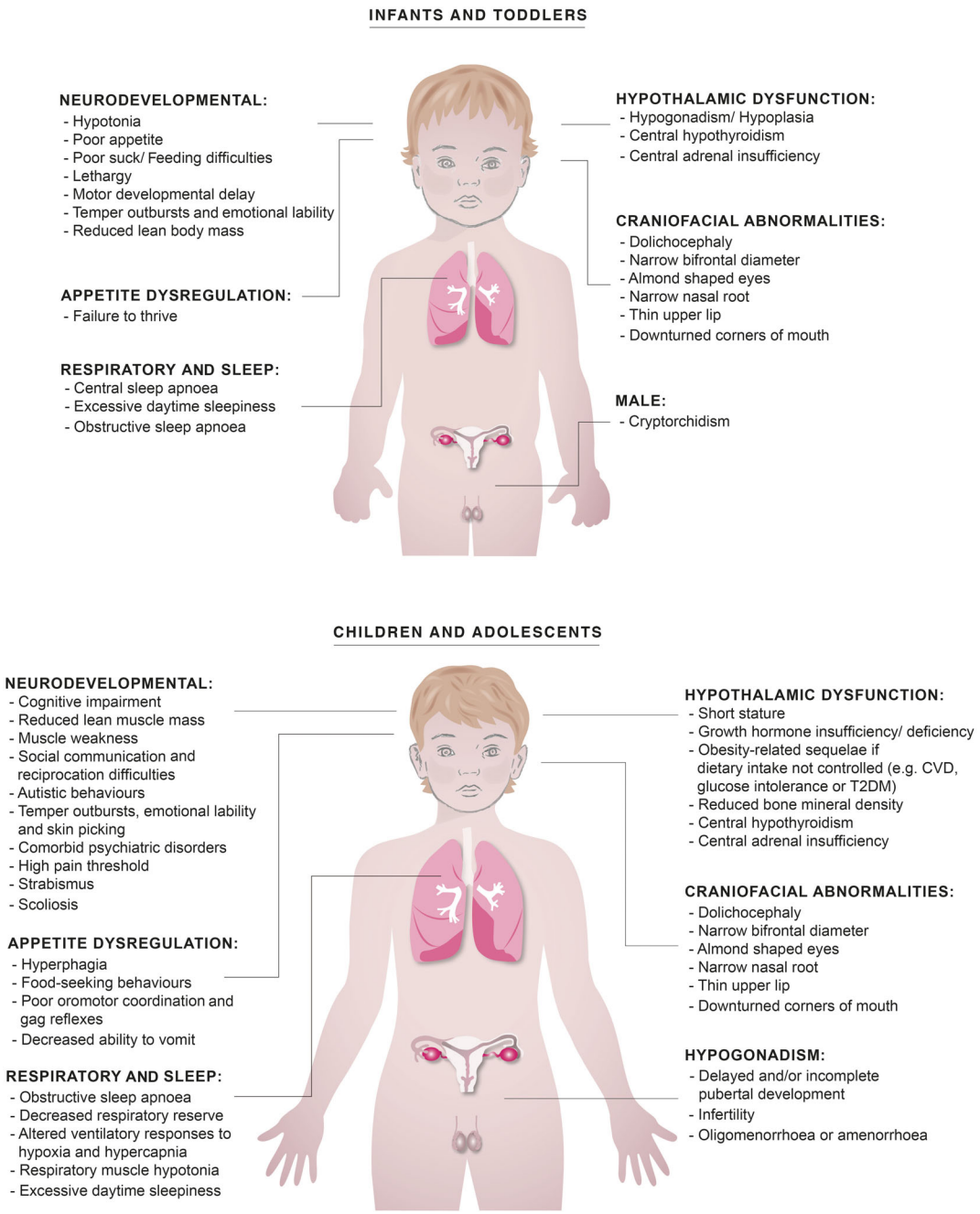

Fig. 1 Characteristic clinical features of the Prader-Willi syndrome phenotype in infants and toddlers under 3 years of age and in children and adolescents aged 3 years and older. CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

children with PWS (n = 61).[19] Obsessive compulsive behaviours include obsessions with health-related issues and compulsions such as skin picking and rearranging objects in the environment for increased order.[19] Mental health symptoms as indicated by scores above the clinical threshold for abnormal behaviours using the Developmental Behaviour Checklist have been observed in approximately three quarters of children and adolescents with PWS.[20] Neurodevelopment and behaviour are also influenced by mutation; a meta-analysis of 744 individuals with PWS found that, in comparison to those with deletions, those with maternal uniparental disomy had higher intellectual quotient scores and greater prevalence of psychosis and bipolar disorders.[21]

Endocrine and metabolic phenotype

Hypothalamic pituitary axis dysfunction is implicated as the underlying disturbance in multiple manifestations of PWS (Fig. 1).[12,22,23]

Growth hormone deficiency

Growth hormone (GH) deficiency is at least in part responsible for the characteristic clinical features of reduced growth velocity, muscle strength, low energy expenditure and obesity in PWS.[2,24] GH therapy improves growth velocity and adult height for individuals affected by PWS and maintains lean body mass with age regardless of GH secretory status at baseline.[2,24,25] The benefits of initiating GH therapy have been demonstrated for infants as young as 2–4 months of age and through early childhood.[26] Currently, many children with PWS receive GH therapy, which lowers the body mass index (BMI) and, on average, provides the capacity to maintain BMI below two standard deviations above the age- and gender-matched reference values of the British 1990 normative growth charts for the duration of therapy.[25,27]

Other benefits appear to include improved cognition[28] and behaviour[29] and improved motor strength and function.[30] There is emerging evidence of the beneficial effects of continuing GH treatment into adulthood, with sustained improvements in body composition, and deterioration of these parameters when GH is discontinued after the attainment of adult height.[31] However, as most adults with PWS do not meet the consensus criteria for adult GH deficiency, they are not eligible for subsidised GH replacement in many jurisdictions, including Australia. The physiological effects of cessation of GH therapy at 18 years of age after many years of continuous therapy during childhood and adolescence are not yet well characterised.

Metabolic disturbances and obesity-related sequelae

From birth, children with PWS have an abnormal body composition with increased fat mass and reduced lean muscle mass. Without strictly supervised caloric restriction and regular exercise, appetite disturbances and physical difficulties predispose the majority of children to child-onset obesity. The Danish National Patient Registry database reported that individuals with PWS (n = 155) were 10 times more likely to be obese and 9 times more likely to be diagnosed with type 2 diabetes mellitus than the matched general population (n = 15 500).[32] The development of obesity and impaired glucose metabolism are linked to various aspects of hypothalamic pituitary axis dysfunction. Abnormalities in hormones influencing appetite regulation and satiety signalling, such as ghrelin or peptide YY, may contribute to the hyperphagia in PWS.[2,23] Obesity contributes to the increased risk of obstructive sleep apnoea, cardiovascular disease, reduced bone mineral density and fracture and scoliosis observed in patients with PWS.[2,32,33]

Hypogonadism

Hypothalamic pituitary axis dysfunction also affects sexual development through hypogonadism, which usually manifests at birth. Almost all males with PWS have unilateral or bilateral cryptorchidism, although hypoplasia of the labia minora and clitoris in girls is less uniformly reported.[22,23] Many children will commence puberty spontaneously but will have incomplete pubertal progression or maintenance without hormone replacement therapy. This results in infertility for nearly all individuals with PWS, although there have been isolated case reports of pregnancies in PWS.[22,23] Untreated hypogonadism contributes to central adiposity and reduced vertebral bone mineral density.[22,34] Sex steroid hormone replacement therapy has important benefits of improving linear growth, bone health and muscle mass and may improve the emotional well-being of adolescents with PWS.[34]

Central hypothyroidism

Cross-sectional studies have reported hypothyroidism in 72.2% of infants under 2 years of age,[35] 6–24% of children and adolescents[36] and at rates similar to the general population in adults with PWS.[37] Longitudinal research assessing the natural course of thyroid levels with a standard approach is required to determine the prevalence of central hypothyroidism across the life-span of individuals affected by PWS and for comparison with the general population. GH therapy may unmask central hypothyroidism in children with PWS, and annual surveillance is recommended.[38]

Adrenocorticotropic hormone insufficiency

Diagnostic tests and criteria for defining central adrenal insufficiency vary, resulting in a reported prevalence of central adrenal insufficiency in PWS ranging from 0 to 60%, with the majority of reports suggesting that it is closest to 10%.[39] Inadequate adrenal response to stress has been suggested as one reason for reduced clinical symptoms observed in individuals with PWS when unwell, and has been hypothesised as a cause of unexplained acute deaths in childhood in PWS.[40] The true prevalence of adrenal insufficiency and the subsequent potential for adrenal crisis in individuals with PWS is currently uncertain.[39]

Appetite dysregulation

PWS is characterised by an age-dependent spectrum of appetite dysregulation, ranging from neonatal feeding difficulties with failure to thrive in infancy to the development of hyperphagia and subsequent obesity. By maintaining clinical records of weight gain and eating behaviours over a 10-year period (n = 58), Miller

Table 2 General phases of altered feeding patterns and growth in Prader-Willi syndrome (adapted from phases described by Miller *et al.*[41])

Phase	Start of phase age range	Description
0	*In utero*	Maternal descriptions of reduced fetal movement, lower birthweight and length
1a	Birth	Difficulty feeding, poor appetite and weight gain
1b	5–15 months Median 9 months	Improved appetite, begins to gain weight along an expected growth curve
2a	18–36 months Median 2 years	Weight crosses curves, no significant increase in appetite or food intake
2b	3–5 years Median 4.5 years	Increased interest in food, greater appetite and caloric intake of food. Children become overweight or obese without dietary intervention
3	Pre-school – teens Median 8 years	Hyperphagia, loss of satiety, obesity without dietary intervention
4	>20 years (rare)	Regain capacity for satiety, hyperphagia declines or disappears

et al. identified seven distinct phases of appetite dysregulation as summarised in Table 2.[41] Without dietary regulation and control over access to food, obesity is likely and usually retained over the life-span of individuals with PWS.[41]

Butler *et al*.[42] found that, despite receiving a diet restricted to 60–80% of normal caloric intake for age and activity, their cohort of children with PWS who did not receive GH (n = 120, aged 3–18 years) had weights varying between the normative 50th centile and above the 97th centile on normative growth charts generated from national growth data by the Centers for Disease Control and Prevention. They also observed that the normative 50th height centile varied between the 75th and 97th growth centiles for their cohort with PWS. These observations suggest that children with PWS have lower caloric requirements for weight maintenance compared with unaffected age-matched peers. Thus, dietary regulation remains an important aspect of management throughout the life-span.[43] However, in addition to lower energy intake, attention to macronutrient composition and adequate levels of fibre, vitamin and micronutrients is important.[44] Children for whom diet is regulated to avoid obesity should be monitored with respect to linear growth.

Hyperphagia may also be associated with inadequate chewing and eating unusual foods and non-food items, contributing to a greater risk of choking and respiratory aspiration.[45,46] Poor oromotor co-ordination and gag reflexes, hypotonia and difficulties producing an adequate cough to expel excess secretions or airway foreign bodies could further explain these increased risks.[45–47] Recent videofluoroscopy swallow studies suggest aspiration is common and often silent in infants with PWS.[48] Examination of family-reported mortality data between 1973 and 2015 for 312 individuals with PWS in USA found that gastrointestinal problems (e.g. perforation), choking and accidents presumed related to food-seeking behaviours accounted for 22% of deaths (10, 6 and 6%, respectively).[33]

Respiratory and sleep phenotype

Craniofacial abnormalities (Fig. 1) and a small naso- and oropharynx are common in affected individuals, resulting in a relatively narrow upper airway.[46] The presence of obesity can further increase upper airway resistance and is another well-known risk factor for obstructive sleep apnoea syndrome.[45] Obstructive sleep apnoea is found in almost 80% of children with PWS,[49] and those with moderate to severe obstructive sleep apnoea exhibit more hypoventilation and more severe desaturation during sleep than typically developing children with a similar severity of obstructive sleep apnoea.[50] This may partly result from decreased respiratory reserve and increased work of breathing in PWS children related to altered ventilatory responses to hypoxia and hypercapnia or comorbidities of obesity and scoliosis.[46] Consequently, children with obstructive sleep apnoea related to PWS may be at greater risk of developing obesity hypoventilation syndrome than other individuals with a similar level of obesity.

Central sleep apnoea is also frequently reported in PWS, particularly in children younger than 2 years of age.[51] Contributors to central sleep apnoea include respiratory muscle hypotonia, abnormal arousal and ventilatory control mechanisms and may also be a downstream effect of hypothalamic dysfunction related to hypocretin deficiencies.[45,46] The presence of excessive daytime sleepiness in individuals with PWS in the context of adequate quality and quantity of sleep, even in the absence of or sufficient treatment for sleep disordered breathing and hypothyroidism, suggests hypersomnolence is related to hypothalamic dysfunction, particularly hypocretin (also known as orexin) deficiencies, causing a narcolepsy phenotype with or without cataplexy.[45,46]

GH treatment can have varied impacts on sleep disordered breathing. GH may worsen obstructive sleep apnoea syndrome symptoms by stimulating adenotonsillar and retropharyngeal lymphoid tissue growth, but on the other hand, symptoms could be alleviated by the beneficial effects of GH on body composition.[52] Although previous observational studies could not demonstrate a consistent increase in obstructive sleep apnoea, it is advised to regularly screen children with PWS on GH using polysomnography due to the risk of progressive obstructive sleep apnoea syndrome in some individuals with potentially severe sequelae.[53] Furthermore, studies to date indicate that GH supplementation may be associated with a reduction in central sleep apnoea, but the observational nature of these studies makes it difficult to differentiate improvements due to the natural history of PWS from effects caused by GH.[53]

Well-being and quality of life

Focus in the literature on neurodevelopmental disorders is shifting to better understand the lived experiences of affected children and their quality of life. The phenotype of PWS is associated with a complex set of physical and psychological needs that challenge the child's daily living, particularly in relation to hyperphagia, social functioning and behavioural difficulties. For example, leisure activities for 123 individuals with PWS (4–48 years) frequently included watching television, particularly those with compulsive behaviours, with limited physical play and activities, particularly those with greater BMI values.[54] Quality of life is a broad descriptor of well-being, and compared with typically developing children, physical, social and mental functioning scores have been reported to be lower for children with PWS (n = 9 younger than 14 years, n = 20 older than 14 years).[55] Similar differences, particularly for psychosocial functioning, have also been observed, with children with PWS (n = 44) receiving lower scores than children with obesity but not PWS.[56] A randomised controlled trial evaluating the effects of GH for children with PWS (n = 26, median (interquartile range) age 8 (7–11 years)) found that benefits for physical functioning were accompanied by better quality of life, which was sustained over an 11-year follow-up period.[57] There is, nevertheless, limited literature on the quality of life in PWS, with interpretation hampered by small sample sizes, use of different measurement tools and lack of multivariate models investigating the determinants of quality of life.

Longer-term social outcomes are of interest to those managing children with PWS who will transition to adult care with time, but the literature in this area is particularly scant. While poorer executive and social functioning has been associated with poorer academic attainment,[15] indicators for employment and accommodation outcomes are not understood. One UK survey published in 1990 found heterogeneous outcomes with 1 in 6 of 61 young adults with PWS achieving employment, albeit in most cases, this was in 'sheltered' employment.[58] Current data across a

population are unknown but are of critical importance for family counselling and for the planning of health and disability supports during and after the transition period from paediatric to adult health services and other supports.

Family and caregiver well-being

Common challenges for caregivers of children with special needs include child sleep disturbances and behavioural and emotional problems, which place demands on caregiver resources and a great strain on family relationships and functioning.[59,60] Delays in diagnosis and accessing ongoing treatments and supports leads to substantial parental stress in many rare genetic disorders.[61] A high prevalence of child sleep disturbances leads to insufficient and disrupted sleep for caregivers,[8] compounding the management of daytime challenging behaviours.[62] Caregiver demands in PWS also include intensive supervision due to the need to limit access to food.[2,63] Excessive food-seeking behaviours have been negatively correlated with maternal life satisfaction ($n = 123$; $r = -0.25$, $P = 0.001$)[64] and are associated with higher levels of family stress.[65] Greater availability of food outside the home environment and difficulties in accessing timely respite with carers who have an adequate understanding of PWS may also restrict social activities.[7,65] Interviews with mothers of children with PWS ($n = 8$) exploring parental stress and coping identified concerns related to meeting their own personal needs and difficulties coordinating education, work placement and other supports from service agencies for their child.[7] Siblings of children with PWS may also experience substantial stress, and necessary supports for them have not been explored.[65]

There is a complex interplay between child and parental well-being. Studies examining this relationship in other chronic childhood conditions have found that challenging child behaviours negatively affected maternal well-being, and maternal depressive symptoms in turn negatively impacted the future behaviour of the child.[66] Research over relatively short time frames has found each to be predictive of the other over 10 months ($n = 72$)[67] and 2 years ($n = 175$).[68] Further research is required to confirm causality and mediating factors within these complex relationships. Current evidence is an insufficient foundation for advocacy and service provision for affected families.

Discussion

PWS is a genetic condition with multiple neurodevelopmental features and comorbidities necessitating ongoing medical and behavioural supervision, intensive management and extensive lifestyle modification by caregivers and families of affected individuals. Current comprehensive and multidisciplinary care using GH and dietary management can help the child with PWS achieve BMI values within normal range, and this is a clinical goal. We have identified gaps in the understanding of musculoskeletal functioning, physical activity and swallowing dysfunction and uncertainty on the effects of GH on respiratory and sleep functioning. GH was approved as a treatment for PWS in 2011, yet guidelines regarding age of initiation, dosage and continuing GH therapy beyond reaching adult height have not been established, producing cohorts with variable use of GH therapy.[24] There is a relatively high prevalence of mental health symptoms, including challenging behaviours, that demands systematic evaluation and management, with implications for child and family well-being and functioning.

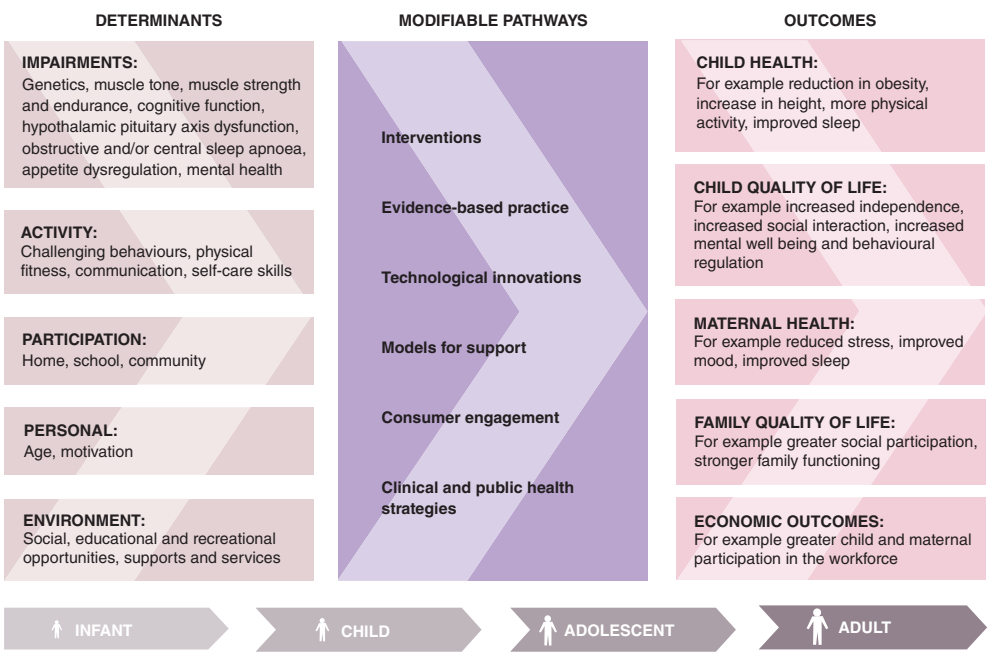

Fig. 2 Model of the determinants and modifiable pathways at the individual, social and socio-economic levels that influence quality-of-life outcomes for children and families affected by Prader-Willi syndrome.

Child and family functioning are intertwined, and the symptoms of PWS can threaten both the child's and caregiver's quality of life. Most studies examining the quality of life for individuals with PWS and their caregivers thus far are limited in the generalisability of their results due to sample sizes or by limited accounting for important covariates. For example, poor sleep, challenging behaviours and the impacts of services to support individuals with PWS and their families are largely omitted from analyses. There have been no studies on school functioning or transition from paediatric to adult health services, and data on young adult employment and accommodation are sparse.

There have been limited Australian studies of PWS.[1,3,7,25,26,62] This gap is particularly relevant for Australian families with the rollout of the National Disability Insurance Scheme where caregivers must provide evidence of therapeutic benefit from supports and services to receive funding for their child. Emotional and educational support from parent support groups has been suggested to moderate the social isolation and reduced quality of life for caregivers with individuals with other chronic conditions[60] but has not been examined in PWS. The Prader-Willi Research Foundation and the Prader-Willi Syndrome Association in Australia are two examples of resources utilised by caregivers for individuals with PWS. Guidance on the implementation of comprehensive multidisciplinary clinics for PWS warrants investigation, including ensuring equity of access for rural and remote families.

We propose that existing gaps in the literature can be addressed by the development of an Australian population-based registry to enable: (i) capture of phenotypic variability; and (ii) inclusion of a comprehensive set of variables with relevant covariates for the evaluation of child and family outcomes (Fig. 2). Successful examples in Australia include the Victorian Cerebral Palsy Registry, which includes individuals born or living in Victoria with cerebral palsy since 1970,[69] and the Australian Rett Syndrome Database, which ascertains individuals with Rett syndrome born since 1976,[70] each capturing a population for surveillance and comprehensive research programmes. To this end, we have initiated the process of creating an Australasian PWS Registry to enable a population-based analysis of variations in phenotype, the treatments and resources available to support the needs of children with PWS and their families and subsequent impacts on child and caregiver quality of life.

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