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The consequences of hyperphagia in people with Prader-Willi Syndrome: A systematic review of studies of morbidity and mortality

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Abstract

Prader-Willi Syndrome (PWS) is a multi-system genetically determined neurodevelopmental disorder and the commonest cause of syndromal obesity. The development of hyperphagia in early childhood is part of the phenotype arising as a result of an impaired neural response to food intake and the inability to regulate food intake in line with energy needs. Severe obesity develops if access to food is not controlled.

In this review we evaluate the evidence for increased morbidity and mortality in PWS in order to establish the extent to which it is directly related to the obesity; a consequence of the eating behaviour itself independent of obesity; or associated with other characteristics of the syndrome.

Medline, Cochrane, PsychINFO, CINAHL, Web of Science and Scopus databases were used to systematically identify published material on PWS and hyperphagia and syndrome–related morbidity and mortality. One hundred and ten key papers were selected. Data on 500 people with PWS indicated that the average age of death was 21 years and obesity was, as expected, a significant factor. However, the behaviour of hyperphagia itself, independent of obesity, was also important, associated with choking, gastric rupture, and/or respiratory illness. Other syndrome-related factors increased the risk for, and seriousness of, co-morbid illness or accidents. We conclude that improving life-expectancy largely depends on managing the immediate non-obesity and obesity-related consequences of the hyperphagia, through improved support. The development of new treatments that significantly reduce the drive to eat are likely to decrease morbidity and mortality improving quality of life and life expectancy.

1. Introduction

Prader-Willi Syndrome (PWS) is a complex genetically determined neurodevelopmental disorder in which multiple organ systems are affected. The birth incidence is approximately 1 in 10,000–25,000(Smith et al., 2003a, Smith et al., 2003b). There are well-characterized early and later phenotypes, and the diagnosis is usually suspected at birth due to the presence of severe hypotonia, failure to thrive, and in boys, undescended testes. Developmental delay, evidence of usually mild intellectual disabilities, the effects of relative sex and growth hormone deficiencies, and a characteristic neuropsychiatric phenotype become apparent during childhood. Supplementary growth hormone treatment is now recommended from early in life(Grugni et al., 2016). A central characteristic is the emergence, in early childhood, of deregulated eating behaviour and the onset of hyperphagia(Angulo et al., 2015). Not all people with PWS will manifest obvious hyperphagic traits and such behaviour varies between people with PWS. PWS is the most common cause of syndromal obesity with approximately 82–98% of people with PWS reported to be overweight or obese(Muscogiuri et al., 2019). It is also the most common genetic cause in humans of potentially life-threatening obesity(Butler and Thompson, 2000). Much of the morbidity and mortality in PWS is considered to be related to the clinical impact of obesity consequent upon the hyperphagia(Butler et al., 2016). Life expectancy for people with PWS is reduced with estimates of a 3% mortality rate per year for those with the syndrome, compared to roughly 1% for the general population in England and Wales(Whittington et al., 2001).

Prader et al. first described what subsequently became known as Prader-Willi Syndrome in 1956. It was not until the 1990s that the genetic basis for the syndrome was fully established. Approximately 70% of people with the syndrome have an interstitial deletion at q11-13 of chromosome 15 of paternal origin, 25% have the presence of a maternal uniparental disomy (mUPD) of chromosome 15, and the remaining 5% have an imprinting centre defect(Cassidy et al., 2012). The gene(s), whose absence of expression results in PWS, are imprinted in humans when inherited from the maternal line and only expressed when inherited from the father. The presence of the above chromosomal abnormalities therefore results in the absence of expression of these gene(s) giving rise to the PWS phenotype.

The mechanisms underlying hyperphagia are not completely elucidated. Observational and neuroimaging studies indicate impairments in the neural mechanisms that mediate the satiety

cascade and feelings of hunger and fullness(McAllister et al., 2011). Although there are trials being undertaken to date there are no drugs that have been licensed to treat the hyperphagia(Crinò et al., 2018). There is guidance about the medical management of PWS(Goldstone et al., 2008) but no formally approved and internationally agreed comprehensive support strategies and there is uncertainty how to respond when an adult with PWS decides they do not wish to live in a food secure environment. The extent of obesity may largely depend on the use or not of measures to ensure food security. Given the significance of hyperphagia in PWS we have in this review also summarized the main management and treatment strategies so as to consider how established approaches might need to be altered to meet the needs of people with PWS and reduce hyperphagia and obesity related morbidity and mortality.

2. Aims of the review

1. To quantify the type and severity of hyperphagia-related morbidity and mortality in people with PWS;
2. To better understand the extent to which hyperphagia-related obesity is the primary driver of morbidity and mortality and/or whether other mechanisms may be significant;
3. To use this understanding to inform and improve health and social care practice in PWS, thereby reducing morbidity and mortality and improving life-expectancy.

The undertaking of this review is part of an initiative by the International Prader-Willi Syndrome Organisation (IPWSO). This initiative also includes a legal analysis of the use of restrictions on access to food, a consultation with different stakeholders using Delphi methodology, and the development of comprehensive guidance.

3. Materials and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(Moher et al., 2015). The Medline, Cochrane, PsychINFO, CINAHL, Web of Science and Scopus databases were searched in January 2020. Publication date and article language were not restricted. We were interested in any

published morbidity and mortality data related to the hyperphagia phenomenon in PWS. The search strategy used was developed by one of the authors (IK), an academic librarian, and is outlined below:

(hyperphagia* or sated or satiety or satiation* or insatiable or appetite or (over adj eat*) or overeat* or ((food* or calorie*) adj2 (seek* or intake)) or (compulsiv* adj2 eat*) or (polyphagi* or megaphagi* or (excess* adj2 (hunger* or eat*))) or ((eat* or feed* or food*) adj3 (behav* or control*))).mp. or exp **HYPERPHAGIA**/or exp **satiation**/or exp **appetite**/or exp **eating behavior**/or exp appetite/or exp **feeding behavior**/or exp energy intake/

AND

*exp **Prader-Willi Syndrome**/or "Prader-Willi".ti,ab. or "Labhart Willi ".ti,ab. or (Royer* adj Syndrome*).ti,ab.*

Fig. 1 is the PRISMA flowchart depicting the article retrieval and selection process. Two independent reviewers screened all abstracts prior to selection or exclusion, using online Rayyan software. All records incorporated for inclusion were evaluated on the basis of their full text, including figures and diagrams. Where there were discrepancies around incorporation of a paper, a third independent reviewer was asked to assess the paper. The range of publications included in this review includes case reports from 1968 to 2020, case series including 2–6 patients from 1992 to 2018, and larger clinical cohort or population based studies from 1974 to 2020.

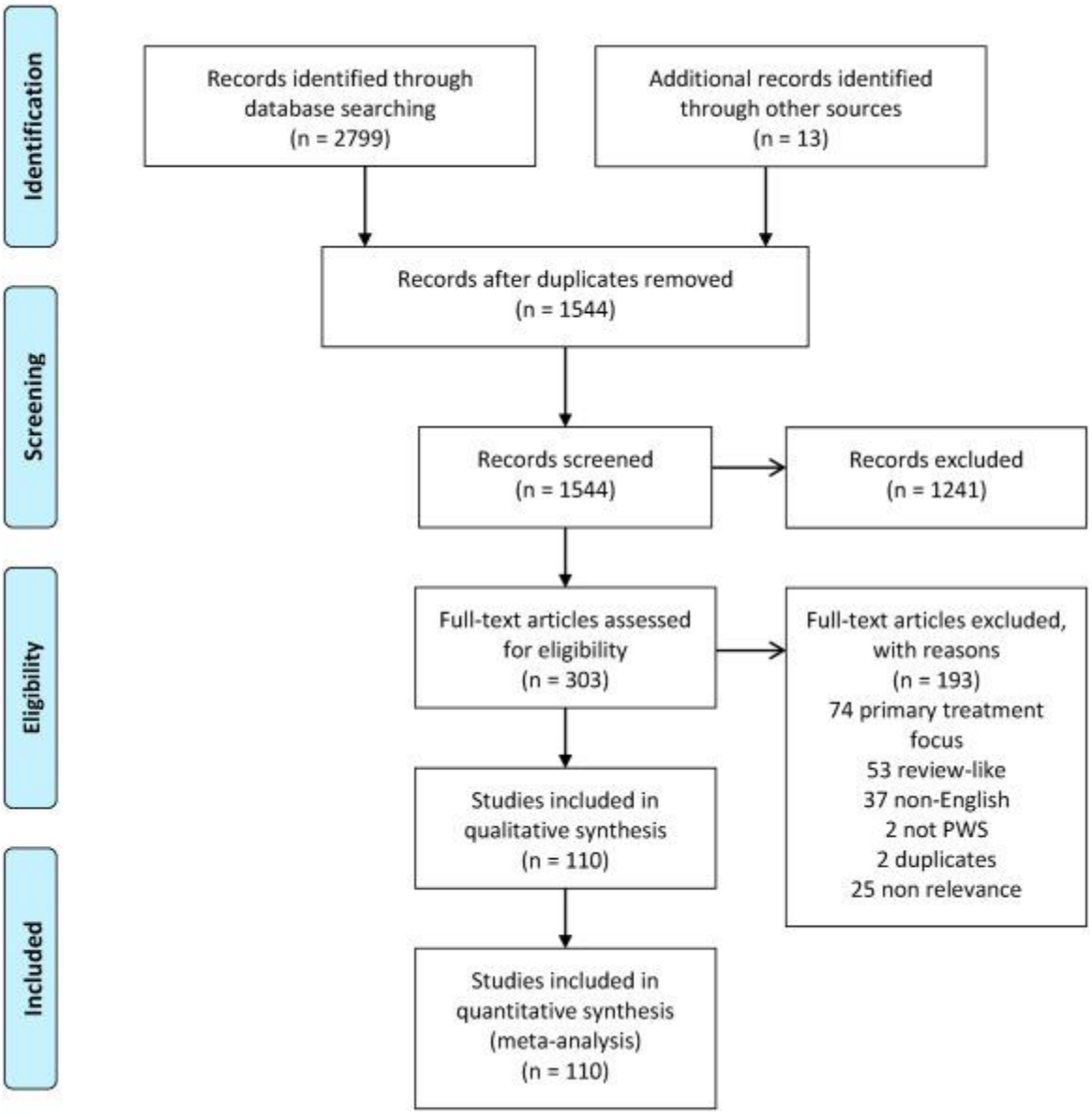

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Fig. 1. *A Prisma flowchart*(Moher et al., 2015) *outlining our search strategy and retrieval process. (Abbreviations n = number).*

To the best of our knowledge, this is the most complete systematic review exploring hyperphagia-related morbidity and mortality in PWS. The data spans a range of evidence of differing quality from large-scale population studies and systematic reviews to case reports.

3.1. Inclusion criteria

- Peer reviewed.

- English language full text.
- Not reviews unless distinct PWS cases included.
- PWS syndrome only.

4. Results

Database searches generated 2799 records. An additional 13 records were identified through other sources. After duplicates were removed, 1544 records were screened for eligibility on the basis of their abstracts. In total, 1241 records were excluded at this stage, and the remaining 303 records were then assessed for eligibility based on their full text. A further 193 were removed for a variety of reasons, including language, non-relevance to the clinical question, and inability to source. A total of 110 studies were included in the final qualitative synthesis and meta-analysis. Most studies were from a small number of high resource countries where there was an evident focus on PWS research, such as Australia, Denmark, France, Italy, Japan, Norway, Sweden, Spain, USA, and UK.

The data in Table 1, which summarizes population and clinic-based mortality studies, indicate that mortality in PWS is generally at a younger age than in people with non-syndromal obesity or in the general population. Average age of death, where mean or median figures were available, was 22.1 years with a range of 0–68 years. One paper estimated a probability of 0.87 of survival to 35 years but obesity significantly increased the risk of mortality(Lionti et al., 2012). Many of the deaths reported were in notably obese individuals suggesting that, in PWS, obesity is a generalized risk factor for early mortality(Bray et al., 1983; Butler et al., 2017; Lionti et al., 2012). Where gender was reported, 55.6% of deaths were in males, 44.4% in females. This finding of increased deaths in males could be partially explained by increased cardiovascular risk in the male population generally, given that PWS is distributed equally between the sexes. There is very limited post-mortem data reported in these studies (Stevenson et al., 2007a; Lionti et al., 2012; Einfeld et al., 2006).

Table 1. Mortality data table. Studies exploring mortality cases in PWS, either population based or clinic based, have been included. Where available post mortem results have also been included, as well as genetic evidence and whether PWS was genomically confirmed in each case.

Paper	PWS patients	Gender	Age	Country	Study Type	Result in terms of mortality	Impact of obe
Pacoricona Alfaro et al. (2019)	104 patients	56 male 48 female	1 month–58 years	France	Mixed	55 cases respiratory failure/infection 15 cases cardiovascular 4 cases GI 4 cases of sepsis 18 cases of sudden death 5 cases unknown 3 other – end stage renal failure, status epilepticus, “strangled”	98% of adults w reported obese (data on obesity v found)
Bray et al. (1983)	40 patients	Unclear Deaths 3 male 1 female	1 month–37 years	USA	Mixed	4 deaths, confirmed by autopsy 1 post intestinal bypass surgery 1 massive PE 1 unknown 1 respiratory difficulties	3 deaths closely with obesity, we 105-201 KG
Butler et al. (2017)	486 patients	263 male 217 female 6 unknown	29.5±16 years	USA	Population based	70% of deaths in adulthood 31% due to respiratory failure (94) Precise cause of death known for 312 cases 50 cardiac 30 GI (perforation, distension, obstruction) 29 infection 22 obesity 19 PE 18 choking 17 accidental 7 renal failure	Average BMI at of death identifi 132 cases and w average was 49±
Craig et al. (2006)	328 patients treated for 1 year, 161 treated for 2 years	3 male 2 female	Median age 6; range 4.7–15.8 years	Australia	Population based	Five sudden death cases Range 3–15 years 3 were obese 1 OSA 1 respiratory insufficiency 1 pneumonia 1 diarrhoea, dehydration, cardiac arrest 1 found dead in bathtub Scoliosis in 24 Hyperglycemia in 4 DM in 6, five of those T2DM	3 were obese we for height >200%
Einfeld et al. (2006)	37 patients	3 male 3 female	20–43 years	Australia	Population based	Six deaths X1 cardiorespiratory failure, morbid obesity X1 cardiomegaly, morbid obesity X2 not known X1 ARDS, possible sepsis, possible aspiration X1 pneumonia, cerebrovascular accident, DM	Deaths in PWS rate as compared control group; B not listed Morbid obesity in ×2 as cause o death
Hedgeman et al. (2017)	155 patients	71 male 84 female	Mean 18 years, standard deviation 17 years	Denmark	Population based	10 deaths from 155 patients; causes not specified 9x more likely to have T2DM than general population 0.6–3.2% vs 0.3% more likely to have a DVT 0.6–3.2% vs 0.0% more likely to have a PE 0.6–3.2% vs 0.2% more likely to have an MI	Ten times more to be obese than general populati ten times more l to die than gener population

Paper	PWS patients	Gender	Age	Country	Study Type	Result in terms of mortality	Impact of obe
						Risk of death significantly elevated RR 11.0 (CI 5.7–21.1 95%) Diabetes significantly increases risk of death RR 26.9 (95%, CI 10.0–72.6)	
Laurance et al. (1981)	24 patients + 9 deaths	13 male 11 female	15–41 years	USA	Clinical based	4 diabetic blood sugar curves, 3 clinically diabetic 9 deaths – 4 autopsied; all cardiorespiratory failure 1 post gastric surgery for obesity with difficulty suturing up the rectus abdominis due to body habitus, died post operatively 1 died post operation for scoliosis	Obesity complic by scoliosis a contributory fac deaths
Lionti et al. (2012)	163 patients	90 male 73 female	3 weeks–60 years	Victoria, Australia	Mixed	15 deaths 1 wound infection 1 endocarditis 1 PE 1 respiratory failure + scoliosis 1 MI and heart failure + OSA 1 PE and underlying T1DM 1 bronchopneumonia + HTN + DM 1 pancreatitis, OSA, cardiac failure, PH 1 PHD 1 respiratory failure 5 not known	Probability of liv 35 years signific lower for obese p = 0.03 "Trend towards higher mortality in individuals w known obesity (5.67; 95% CI: 0. 62.21)" BMI range at de 11.7–69.4 kg/m²
Manzardo et al. (2018)	486 patients	263 male 217 female 6 unknown	Unknown	USA	Population based	Precise cause of death known in 311 cases Most common cause respiratory failure Increase in accidental death observed in males Cardiac deaths 15/57 in early cohort 36/254 in later cohort PE and GI complications listed also as causes of death Accidental deaths in males increased in recent cohort	Improvement in cardiorespirator death from early cohorts, postulat to more obesity control
Nagai et al. (2005)	20 patients	14 male 6 female	0–34 years	Japan	Clinic based	6 deaths in non-infant cohort ranged 14-34 3 male 3 female Cellulitis in lower leg x1 PE x1 PE and renal and heart failure x1 X1 renal and heart failure Tub drowning ×2 due to respiratory weakness	BMI 16.2–45.7
Schrander-Stumpel et al. (2004)	27 patients	21 male 6 female	0–68 years	The Netherlands	Mixed	14 children over 5 years old 10 deaths listed as related to obesity including MI, abdominal fistula, cardiac arrest, acute gastric dilatation and CVA 13 male, 1 female, (3 had autopsies)	10 deaths listed potentially relate obesity by the pa
Smith et al., 2003a, Smith et al., 2003b	36 patients	18 male 18 female	Mean age 26 years,	Australia	Clinic based	10 deaths 60% related to heart failure, stroke, coronary artery disease	BMI 32.7–52.2 Suggestions that thorough heart s

Paper	PWS patients	Gender	Age	Country	Study Type	Result in terms of mortality	Impact of ob
			range 14–48			X1 sudden collapse X1 pneumonia X1 hypoglycaemia X1 coronary occlusion X1 stroke X1 PE X1 cardiac and respiratory failure X1 not determined X1 post-operative complications X1 congestive cardiac failure 100%of living patients had sleep apnoea 19% of living patients had diabetes mellitus	is needed in the term manageme PWS patients BMI 41.2 for de group 42.6 for UPD gr
Stevenson et al. (2004)	10 patients	4 male 6 female 2 adults (others 3.5 years and below)	5 months–43 years	USA	Mixed/clinic based	2 adult deaths 1 tub drowning due to hypersomnia 1–29 year old male, acute and chronic aspiration pneumonia, mild obesity on autopsy 2–43 year old female, HTN, weight 159 kg, two previous episodes of pneumonia, insulin dependent diabetes no autopsy	Significant weig comorbidities, ri accidental death
Stevenson et al. (2007a)	152 patients	6 male 2 female	Age at death 17–49 years	USA	Mixed – via questionnaire	4 deaths due to gastric rupture 2 autopsy 2 familial report A further 2 males and 2 females suspected to have gastric rupture and necrosis, three with hematemesis.	One death due to gastric rupture w after binge eatin BMI range 22–5 4 obese, 2 not kn 2 normal weight
Stevenson et al. (2007b)	152 patients	11 male 1 female for choking death	Average age 31.4 years; ranging 1–55 years	USA	Mixed – via questionnaire	24% of patient cohort died due to respiratory compromise/pneumonia 8% of deaths were due to choking 63% had sleep apnoea 6% required Heimlich manoeuvre in past 34% of cohort had history of choking	12 deaths due to hyperphagia and choking Average weight death 100.3 kg
Tauber et al. (2008)	64 patients	42 male 22 female	0–19 years	France	Population based	64 deaths in children, review 61% respiratory disorders Most deaths under 2 years (61%) 3 deaths due to food choking	Prevalence of ob in 27/64 deaths
Vogels et al. (2004)	78 patients	39 male 39 female	0–56, years; mean age 26	Flanders	Mixed	7 deaths 1 pneumonia high temperature 2 sudden collapse; recurrent respiratory infections 3 acute onset pneumonias 4 complicated abdominal hernia 5 car accident 6 cerebrovascular stroke 7 cardiorespiratory failure	No data on BMI note complex abdominal herni

(Abbreviations, GI = gastrointestinal, PE = pulmonary embolus, OSA = obstructive sleep apnoea, DM = diabetes mellitus, T2DM = type two diabetes mellitus, ARDS = acute respiratory distress syndrome, BMI = body mass index, Xn = number of cases, RR = relative risk, CI = confidence interval, PHD/PH = pulmonary hypertensive disease/pulmonary hypertension, CVA = cerebrovascular accident, HTN = hypertension).

Data was extracted and summarized from most of the papers listed in Table 1 identifying in total 500 cases where the cause of death was clear. The most common cause of death was respiratory failure (177/500; 35%); cardiovascular causes were the second most commonly documented cause of death (84/500; 16.8%); and there were 25/500 (5%) cases of pulmonary embolus; 40/500 (8%) gastrointestinal related causes of death, and 38/500 (7.6%) cases of sepsis or non-pneumonia infections contributing to the cause of death. Twenty-one (4.2%) of the deaths were listed as 'sudden death or collapse', 15/500 (3%) unknown, 3/500 (0.6%) perioperative, 10/500 (2%) due to end stage renal failure, 22/500 (4.4%) listed as purely obesity-related, and 5/500 (1%) miscellaneous. In most of these 500 cases the individuals with PWS had been clinically obese prior to death, and where BMI data was reported, 69% fell in the obese category or above. There were also documented cases of the following: unusual deaths secondary to choking (30/500; 6%); drowning in the bath (4/500; 0.8%); and accidental death (18/500; 3.6%) (Stevenson et al., 2004, 2007b; Nagai et al., 2005; Butler et al., 2017; Craig et al., 2006). These causes of death were not directly linked to obesity per se, although several of the people with PWS were obese, but the cause was more directly related to the behaviour of hyperphagia. We note in Table 2 that in one study toxin ingestion was reported as 12 times more common in people with PWS than in the general population(McCandless et al., 2012), again possibly highlighting the consequences of the behaviour of hyperphagia itself. In those cases listed in Table 2 and also in the case reports reviewed there is evidence of high perioperative mortality after bariatric surgery(Bray et al., 1983; Laurance et al., 1981). In the 18/500 cases of accidental death, notably there was one case of a car accident(Vogels et al., 2004). Although in this case there is no documented reason for the accident in the paper, the authors noted an increased mortality after 30 years.

Table 2. Morbidity cohort table. Studies with PWS cohorts of above 6, which outlined different aspects of morbidity, have been included, including salient trials that featured in our literature search, if BMI and patient data was of sufficient quality.

Author	PWS patients	Gender	Age	Country	Result in terms of obesity
Akefeldt (2009)	47 patients	28 male 19 female	2–40 years	Sweden	Unusual high amounts of water intake in 7 individuals associated with hyponatremia, mostly in non-deletion group; Matched with controls
Allas et al. (2018)	47 patients	23 male 24 female	Mean 26.8; range 3–44 years,	Spain, France and Italy	Median BMI 38 kg/m^2 in cohort Median hyperphagia severity score 4.49/7
Alyousif (2019)	764 patients	Not included	Not included	USA	Constipation, diarrhoea and stomach pain is significantly higher in PWS patients if BMI is increased ($p < 0.05$, $p < 0.001$, $p < 0.05$) Acid reflux decreased with BMI ($p < 0.01$)

Author	PWS patients	Gender	Age	Country	Result in terms of obesity
Bailleul-Forestier et al. (2008)	15 patients	10 male 5 female	3–35 years	Belgium and France	BMI range from 16 to 42.6 kg/m^2 in the cohort Evidence of severe tooth caries but not associated with BMI
Beange and Caradus (1974)	15 patients	10 male 5 female	Infancy – more than 10 years	Australia	10/15 patients over 90th percentile in weight
Bellicha et al. (2020)	10 patients	10 female	Mean age 28.8 years	France	Increasing physical activity study Mean BMI 37.2 kg/m^2 in cohort pre-intervention
Brambilla et al. (2011)	109 patients	58 male 51 female	2–18 years	Italy	50 PWS patients were obese, 59 not obese Hypertension in 32% 16/50 p = 0.003 Hypertriglyceridemia in 13/50 p = 0.026 Low HDL-C in 9/50 PWS patients p = 0.001 4 cases of T2DM in obese PWS patients, no other cases elsewhere An average BMI in obese PWS patients of 32.5 kg/m^2
Butler et al. (2002)	66 patients	40 male 26 female	0–46 years	USA	12% prevalence of non insulin dependent diabetes mellitus 3% prevalence of hypertension 3% prevalence of other diagnosed cardiac illness 11% prevalence leg oedema or ulceration 46% prevalence of respiratory problems 15% prevalence of respiratory illness requiring hospital treatment Mean BMI in PWS with diabetes is 37 kg/m^2
Butler et al. (2019)	103 patients	Vanderbilt cohort: 20 male 27 female UCI cohort: 29 male 29 female	Vanderbilt cohort: 10–44 years UCI cohort: 3–38 years	USA	Mean BMI Vanderbilt cohort is 33.9±8.2 for deletion subtype 33.8±9.1 for disomy subtype Mean BMI UCI cohort is 26.6±8.2 for deletion subtype 23.7±7.4 for disomy subtype
Caldwell et al. (1986)	11 patients	6 male 5 female	14–32	UK	Weight of 4 subjects over 90 kg Weight 58.64–113.64 kg
Coupaye et al. (2016)	73 patients	35 male 38 female	Mean age 25.5 years ± 8.9	France	19% of cohort had T2DM BMI mean 40.9 kg/m^2 in deletion group; BMI mean 34.6 kg/m^2 in UPD group HBA1C mean 5.6% in deletion group; HBA1C mean 5.3% in UPD group Hypertriglyceridemia in 5 deletion group patients and 1 UPD patient High LDL in 6 deletion group patients and 1 UPD patient
Dykens (2000a)	100 patients	Not included	4–46 years	USA	Skin picking in 97% of cohort Hyperphagia in 98% of cohort
Dykens (2000b)	50 patients	28 male 22 female	Mean age 25.75±8.38 years	USA	Mean BMI 32.55 for PWS cohort 2/5 of PWS cohort likely to endorse eating inedible food combinations; matched with controls

Author	PWS patients	Gender	Age	Country	Result in terms of obesity
Einfeld et al. (2014)	30 patients	20 male 10 female	12–30 years	Australia	RCT for oxytocin nasal spray Sleep apnoea present in 8 of the cohort
Feighan et al. (2020)	61 caregivers of PWS patients	26 male 35 female	Mean age 16.3 years; range 11 months–51 years	Ireland	11% of cohort prevalence of PICA 76% prevalence of skin picking 16% prevalence of inserting objects 81% prevalence of hyperphagia
Gavranich and Selikowitz (1989)	22 patients	11 male 11 female	<1–39.1 years	Australia	Persistent skin picking in 81% of cohort T2DM present in 2 females
Greenswag (1987)	232 patients	115 male 117 female	16–64 years	USA, Canada, England, Australia	Severe enough obesity in 11 cases for gastric bypass operation 17% prevalence of hypertension 1 stroke in 24 year old male PWS patient 44 (19%) patients developed diabetes mellitus 29 patients needed insulin to control diabetes mellitus Skin picking in 8% of cases
Grolla et al. (2011)	53 patients	28 male 25 female	13–42 years	Italy	Mean BMI 38.7 kg/m^2 on admission prior to rehabilitation program
Hauber et al. (2013)	8 patients	5 male 3 female	21–41 years	Germany	BMI mean 29.9±4.8 kg/m^2 on first survey HBA1C mean 6.3±1.3 on first survey Triglycerides 111.3±50.3 mg/dL on first survey 6/8 of the cohort had diabetes mellitus 2/8 of the cohort were on antihypertensive medication
Hoffman et al. (1992)	18 PWS homes	Not included	Not included	USA	Pica in 7/18 homes hoarding and food stealing in 12/18 homes
Höybye (2004)	19 patients	10 male 9 female	17–37 years, mean 25 years	Sweden	Mean BMI of cohort 35.6 kg/m^2 4 patients had impaired glucose tolerance 9 had indications of insulin resistance 7 had moderate dyslipidemia GH can have beneficial effects on body composition in PWS
Jauregi et al. (2013)	100 patients	44 female 56 male	18–53 years	Spain and France	Mean BMI of cohort 42 kg/m^2 Similar hyperphagic questionnaire scores to other studies
Kimonis et al. (2019)	13 patients	8 male 5 female	Mean 15.5±2.9; range 11–21 years	California	Clinical trial diazoxide choline controlled release Mean BMI 38.1±10.9 kg/m^2; Mean per cent body fat = 51.7% (Note criteria to incorporate patients with high body weight)
Meinhardt et al. (2013)	41 patients	19 female 22 male	0.4–12.2 years	Switzerland, Denmark and Germany	Efficacy and safety of norditropin treatment Sleep apnoea was reported in 3 patients Mean BMI of PWS patients 38 kg/m^2
McCandless et al. (2012)	130 patients	66 male 64 female	2–18 years	USA	12 fold increased risk of toxin ingestion compared to general population; matched 20% of PWS subjects had history of toxin ingestion compared to 2% of controls.

Author	PWS patients	Gender	Age	Country	Result in terms of obesity
McCandless et al. (2017)	107 patients	56 male 51 female	12–65 years	USA	Beloranib trial; Mean BMI of cohort 38.2–41.4 kg/m^2, depending on study arm Note criteria is BMI above 95th percentile for age and sex Skin picking in 74% of cohort T2DM in 9% of cohort
Motaghedi et al. (2011)	10 patients	Not included	19.5–36.3 years	USA	RCT for rimonobant; Mean BMI of cohort 42.89±8.90 kg/m^2
van Nieuwpoort et al. (2018)	15 patients	4 male 11 female	19.2–42.9 years	Netherlands	Bone mineral content significantly lower compared to controls BMI higher compared to controls – average 27.5 kg/m^2 $p < 0.05$ Higher prevalence of osteopenia and osteoporosis in PWS group; Matched with controls
Patel et al. (2007)	9 patients	8 male 1 female	28±3 years	Australia	Mean BMI 42.1 kg/m^2 $p < 0.01$; 7 patients were obese 1 patient had experienced a prior cerebrovascular event 2 patients had diabetes mellitus 2 patients had impaired glucose tolerance Matched against controls
Pignatti et al. (2013)	31 patients	14 male 17 female	18–44	Italy	Skin picking in 77.42% of cohort 80.65% of cohort displayed excessive food intake 3.23% of cohort ate non-edible food (PICA) Mean BMI of cohort 45.58 kg/m^2
Shriki-Tal et al. (2017)	53 patients	32 male 21 female	Mean 23.6 years	Jerusalem	35% incidences of skin picking Female predominance for skin picking $p = 0.025$
Sinnema et al. (2011)	103 patients	50 male 53 female	18–66 years	The Netherlands	Mean BMI 32.2 kg/mg^2, 56% prevalence of obesity 9% prevalence of HTN 17% prevalence of diabetes mellitus 45% prevalence of fractures 16% prevalence of osteoporosis 55% prevalence of leg ulcerations or oedema
Young et al. (2006)	19 patients	7 male 12 female	1–50 years	USA	3 participants ate disproportionate amount of the food available BMI non-consumer group (i.e. group that did not eat any of the food placed) 40.5 kg/m^2 and of consumer group was 24 kg/m^2 Evidence of PICA
Saeves et al. (2012)	49 patients	25 male 24 female	6–40 years	Norway	Higher tooth ware loss in PWS Cross matched with population $p < 0.001$ VEDE scores
Saeves et al. (2018)	29 patients	12 male 17 female	3–48 years	Norway	GORD in PWS can lead to severe tooth wear in PWS 31% prevalence of sleep apnoea in cohort 31% prevalence of obesity in cohort

Author	PWS patients	Gender	Age	Country	Result in terms of obesity
					52% prevalence of pathological reflux in cohort
Sanjeeva et al. (2017)	34 patients	23 male 11 female	1–24 years	India	59% prevalence of obesity in total cohort 67% prevalence of hyperphagia 50% prevalence of impaired glucose tolerance 67% prevalence of sleep related problems 67% prevalence of skin and rectal picking 67% prevalence of OSA in school-age cohort 60% prevalence of daytime somnolence in school-age cohort
Sarimski (1996)	28 patients	Not included	97.2 months; range 26–300 months	Germany	Choking in 9.4% of cohort at mealtimes p = 0.01 Gagging in 6.2% of cohort at mealtimes p = 0.012
Sode-Carlsen et al. (2012)	46 patients	21 male 25 female	16–41 years	Norway, Denmark and Sweden	Median BMI 27.2 kg/m^2; 17 patients were obese 7 patients had T2DM 10 patients impaired glucose tolerance Genetically verified PWS; Matched against controls
Sze et al. (2011)	8 patients	5 male 3 female	30±2.8 years	Australia	Exenatide study; mean BMI in cohort 37.4 kg/m^2 4 patients in cohort had T2DM
Yee et al. (2007)	19 patients	14 male 5 female	14–45 years	Australia	4 patients in cohort have obstructive sleep apnoea 9 patients in cohort have obesity hypoventilation syndrome 95% of cohort had TRDI of greater than 5 events per hour; Matched with controls

(Abbreviations, BMI = body mass index HDL-C = high density lipid cholesterol, T2DM = type two diabetes mellitus, RCT = randomised control trial, HTN = hypertension, GORD = gastro-oesophageal reflux disease, TRDI. = total respiratory disturbance index).

Some of the paediatric cases identified were not included in this review as they typically exhibited more commonplace causes of paediatric mortality in individuals below the age of 5 years, however some also exhibited a pattern of unexplained death(Stevenson et al., 2004) and accidental death(Schrander-Stumpel et al., 2004). More generic causes of paediatric deaths in young PWS individuals included cases of sudden infant death syndrome, diarrhoea and rotavirus(Nagai et al., 2005). Notably, reviews focusing on paediatric deaths imply an increased risk of death throughout life from the behaviours associated with hyperphagia, notably choking(Tauber et al., 2008).

The morbidity data in Table 2 indicate that people with PWS are vulnerable from childhood to the cardiovascular sequelae of extreme obesity, with an increased prevalence of hypertension,

diabetes mellitus, stroke, pulmonary disease, and sleep apnoea in these relatively young cohorts(Butler et al., 2002; Sinnema et al., 2011; Sanjeeva et al., 2017; Greenswag, 1987). Studies with an endocrine focus have also indicated, not just a high prevalence of diabetes mellitus, but also a notable high prevalence of impaired glucose tolerance, insulin resistance, dyslipidemia, and hypertriglyceridemia, relative to controls(Brambilla et al., 2011; Coupaye et al., 2016; Hauber et al., 2013; Höybye, 2004; Patel et al., 2007).

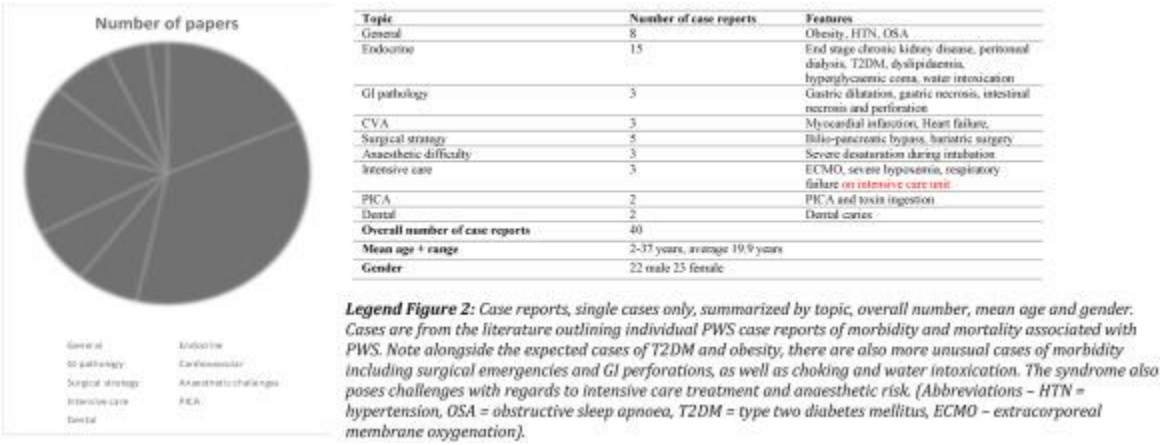
A lifetime of poor health is often an inevitable feature of PWS with morbidity affecting not just the heart, lungs and endocrine system but also the teeth, skin, gastro-intestinal and musculo-skeletal systems. Skin and rectal picking are reported as common in the syndrome(Dykens, 2000a; Feighan et al., 2020; McCandless et al., 2017; Sanjeeva et al., 2017; Pignatti et al., 2013), which, together with a high risk of leg oedema and ulceration(Butler et al., 2002; Sinnema et al., 2011), make people with PWS vulnerable to dermatological infections. There are also notable studies highlighting the impact on bone health(van Nieuwpoort et al., 2018; Sinnema et al., 2011) with PWS patients having lower bone density and higher risk of osteoporosis secondary to the general population. Several clinical trials have also highlighted the high incidence of obesity in people with the syndrome. However, such trials may require a BMI in the obese range or above as part of their inclusion criteria. (Brambilla et al., 2011; Motaghedi et al., 2011; McCandless et al., 2017; Kimonis et al., 2019).

The case report data summarized in Table 3 and Fig. 2 indicate that there are implications of these observations for many medical and surgical specialties, including endocrinology, anaesthesia, intensive care, surgery, medicine, dentistry, paediatrics, neonatology and psychiatry. Surgical emergencies secondary to hyperphagia, including gastrointestinal rupture and necrosis, have been a frequently published cause of morbidity and mortality(Blat et al., 2017; Min et al., 2015; Wharton et al., 1997). There is also an elevated risk with respect to the anaesthetic management of people with PWS in that they are more difficult to intubate and ventilate for bariatric surgery(Legrand and Tobias, 2006). Bariatric surgery appear to be used frequently in countries with limited resources for people with PWS who have severe co-morbidities resulting from extreme obesity secondary to hyperphagia. Such surgery in people with PWS has mixed results(Franco et al., 2018; Laurent-Jaccard et al., 1991).

Table 3. Case series table, featuring cohort reports/cases series with between 2 and 6 PWS patients in each report. .

Case series	Cases	Summary	Theme
Antal and Levin (1996)	2 PWS patients, 13 female and 22 years old male	Both patients excessive obesity, severe respiratory distress, daytime somnolence, limited mobility, BMI 47.56 and 61 kg/m^2 respectively, both underwent bilio-pancreatic diversion, significant weight loss post operatively	Surgical strategy
Braha (2013)	5 PWS patients, four females 1 male, aged 5.5–19	Hypertriglyceridemia in 3 patients, hypercholesterolemia in 2 patients	Endocrine
Franco et al. (2018)	2 male 2 female patients (looking at DBS)	Mean BMI 39.6 kg/m^2, two had previously had bariatric surgery	General, surgical strategy
Itoh et al. (1995)	2 PWS patients, 11 year old female, 15 year old female	OSA, BMI 36 and 43.7 kg/m^2 respectively	General
Laurent-Jaccard et al. (1991)	3 PWS patients, 22 year old male, 40 year old male, 21 year old female	Obesity in two, BMI 25.7, 51.6 and 34 kg/m^2 respectively, use of bilio-pancreatic diversion	Surgical strategy
Legrand and Tobias (2006)	4 PWS patients, 4 months–12 years old	Ventilatory difficulties and anaesthetic complications	Anaesthetic complications
Michalik et al. (2015)	2 PWS patients, 25 year old female 18 year old female	Obesity, case 1 BMI 55 case 2 BMI 64 kg/m^2, case 2 had hypertension, diabetes and asthma; both underwent bilio-pancreatic diversion	Surgical strategy
Lima et al. (2016)	5 PWS patients, 6–16 years	Obesity, mean BMI 37 kg/m^2	General
Tu et al. (1992)	3 PWS patients, all 15 and male	Obesity, Case 1 235 pounds, case 2 148 pounds, case 3 192 pounds	General
Wharton et al. (1997)	6 PWS patients, all female, 3.5–37 years	Gastric distension, necrosis, sepsis, DIC, 1 patient died from sepsis, 1 from cardiac arrest	GI pathology, death

(Abbreviations, BMI = body mass index, OSA = obstructive sleep apnoea, GI = gastrointestinal).



Topic	Number of case reports	Features
General	8	Obesity, HTN, OSA
Endocrine	15	End stage chronic kidney disease, peritoneal dialysis, T2DM, dyslipidaemia, hyperglycaemic coma, water intoxication
GI pathology	3	Gastric dilatation, gastric necrosis, intestinal necrosis and perforation
CVA	3	Myocardial infarction, Heart failure,
Surgical strategy	5	Bilio-pancreatic bypass, bariatric surgery
Anaesthetic difficulty	3	Severe desaturation during intubation
Intensive care	3	ECMO, severe hypoxaemia, respiratory failure on intensive care unit
PICA	2	PICA and toxin ingestion
Dental	2	Dental caries
Overall number of case reports	40	
Mean age + range	2-37 years, average 19.9 years	
Gender	22 male 23 female	

Legend Figure 2: *Case reports, single cases only, summarized by topic, overall number, mean age and gender. Cases are from the literature outlining individual PWS case reports of morbidity and mortality associated with PWS. Note alongside the expected cases of T2DM and obesity, there are also more unusual cases of morbidity including surgical emergencies and GI perforations, as well as choking and water intoxication. The syndrome also poses challenges with regards to intensive care treatment and anaesthetic risk. (Abbreviations – HTN = hypertension, OSA = obstructive sleep apnoea, T2DM = type two diabetes mellitus, ECMO – extracorporeal membrane oxygenation).*

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It is evident from the literature that diabetes mellitus, hypercholesterolemia, and kidney disease are also commonplace in obese individuals with PWS, with reports of end stage kidney disease secondary to type 2 diabetes mellitus(Anno et al., 2019). Cardiovascular emergencies including strokes and myocardial infarcts in young individuals with PWS have been reported(Brás et al., 2018; Paisey, 2011). Poor dental care and its impact on dentition is described in both the case reports and larger studies(Song et al., 2015; Saeves et al., 2012). Poor dentition may contribute to choking.

4.1. Treatments

Table 4 outlines the various treatment and strategies used in the management of hyperphagia, which have featured in the systematic review search. There have also been a recent clinical trials of pharmaceutical agents directed at the hyperphagia – these are listed in Table 4. These medications being trialled have various modes of action and whether or not there is an effect may provide some insight into the underlying mechanisms resulting in hyperphagia. For example, the trials have included the following: Beloranib, a Met2AP2 inhibitor, that resulted in definite improvements in hyperphagia scores but the agent was withdrawn due to unacceptable side effects(McCandless et al., 2017), intranasal carbotocin (an analogue of oxytocin) that resulted in some improvements in hyperphagia and behaviour scores(Dykens et al., 2018), and another (livoletide, an unacylated ghrelin analogue) was withdrawn due no significant effects in the phase 2b trial. Trials of other agents are on-going.

Table 4. Treatments/interventions to reduce the hyperphagia and obesity in PWS.

Pharmacological	Surgical	Other
Beloranib*	Bilio-pancreatic diversion	PWS specific residential home
Caralluma fimbriata	Gastric bypass/Roux en Y	Food security limiting access to calories
Diazoxide Choline Controlled Release (DCCR)	Gastroplasty	Close supervision
Exenatide	Intragastric balloon	Diet and exercise
Fenfluramine*	Bariatric surgery	Gut microbiota diet
Liraglutide	Transcranial DC current deep brain stimulation	Various psychological/behavioural strategies, i.e. function-based differential reinforcement, Psychotropic medications including SSRIs

Pharmacological	Surgical	Other
Livoletide	Vagus nerve stimulation	
Naloxone		
Octreotide		
Oxytocin/carbetocin		
Tesofensine		
Topiramate		

The treatments listed above have varied modes of action and have been trialled or mentioned in the literature. Some have been had evidence of beneficial effects but were discontinued due to side-effects*. None are as yet approved for treating the hyperphagia in people with PWS. (Abbreviations, DC = direct current, SSRIs = selective serotonin reuptake inhibitors).

The use of growth hormone supplementation has the largest evidence basis in terms of promoting growth and a healthier body composition(Grugni et al., 2016). However, there is no evidence that growth hormone impacts on eating behaviour. Antipsychotic and antidepressant medication are used for behaviour problems and/or mental ill health. There is no evidence that they improve the hyperphagia and it is likely that some of these medications make the hyperphagia worse.

Although there are no trials that have explicitly compared outcomes in those who live in food restricted versus non-food-restricted settings, the mainstay of intervention continues to be management strategies that limit the possibility that this marked propensity to hyperphagia will result in obesity. The evidence points to food secure environments and regular exercise as being key to the prevention of obesity. Whilst parents can be expected to adapt the family environment to control access to food this becomes more of a challenge in adult life with increasing independence and difficulty on the part of some adults with PWS to accept restrictions (Hawkins et al., 2011).

5. Discussion

The papers included in this systematic review range from cohort to case studies. Each are valuable, the former providing insights into the main causes of morbidity and mortality in groups that are representative of the population of people with PWS and the latter providing a more detailed insight into individual and, in some cases, unusual causes of death. We have combined data from 14 different studies and many of our conclusions are based on the data from the 500 deaths in total. Some of papers included are from many years ago and there is

likely to be cohort effects in that, for many countries, the availability of early and accurate diagnosis in recent years, combined with improved knowledge about the syndrome, will have resulted in better management, particularly with respect to the transition from the hypophagia of the early phenotype to the hyperphagia of the later phenotype. In addition, the studies are from different countries where the may well have been differences in the availability of diagnostic and support services and in health and social care practices. These may well have had an effect on outcomes.

There is clearly strong evidence from studies from different countries of a significant increase in morbidity and mortality and reduced life-expectancy for people with PWS, compared to the general population. This increase in morbidity and mortality is apparent certainly from early in adult life and increases further with age. What are the reasons for this and what are the implications for treatment and for care? Although there is an overlap between the groups, we propose that this increased risk can be divided into four groups, three of which have implications for intervention specifically with respect to people with PWS. The distinctions between groups outlined below and in Table 5 may be useful when considering prevention. There are the longer-term problems that arise through obesity and the more acute issue around access to food and the risk of choking, aspiration, and the possibility of major life-threatening events, such as stomach rupture.

Table 5. Mortality data summarized and implications. Causes of death is listed for the 500 documented cases where cause of death was clear in this cohort. They are also categorised in terms of whether the causes are obesity or hyperphagia related, or neither. Some causes can be related to some facet of PWS, but neither obesity nor hyperphagia related. Please note that a small number of patients had more than one cause of death was listed.

Groups	Causes of death	Implications
A Directly related to the high rates of obesity that are a consequence of unrestrained hyperphagia.	Diabetes (3/500) Extreme obesity (22/500) Perioperative (3/500) Respiratory failure 177/500 Cardiovascular causes 84/500 Pulmonary embolism 25/500 Obstructive sleep apnoea 1/500	These deaths may have been prevented if obesity could have been prevented. Food security is the only established means of achieving this at present.
B Directly related to the hyperphagia independent of obesity	Choking (30/500) GI perforation/necrosis 40/500 Toxin ingestion Water intoxication	These deaths may be more difficult to prevent as they require being aware of risks and ensuring an environment that effectively manages these risks
C Potentially related to the broader phenotype of PWS, unlikely to be directly related to hyperphagia or obesity	Sudden death 21/500 Accidental death 18/500 Drowning in bath 4/500 Sepsis/infection 38/500 Hypothermia 3/500 ESRF 10/500	The reasons for these deaths may overlap with the categories above but could have been prevented if those providing support were aware of risks

Groups	Causes of death	Implications
	Respiratory hypotonia leading to respiratory death in non-obese infants/SIDS	
D Miscellaneous	Unknown 15/500 Malignancy 5/500 Drug reaction 3/500 Neurological 7/500 Strangled 1/500	Some are risks common to everyone others (such as those in later life) may indicate a specific risk for age-related deterioration.

(Abbreviations GI = gastrointestinal, ESRF = end stage renal failure, SIDS = sudden infant death syndrome).

In group 1 the causes of death can be seen as a direct consequence of the obesity that results from unconstrained hyperphagia. It is essentially the severe obesity that drives the morbidity and mortality. The pattern of obesity observed in people with PWS differs from that of non-syndromal obesity often affecting individuals at a much younger age and also appears more resistant to established means of prevention and control. Cardiovascular and respiratory diseases, including pulmonary emboli, are the most prevalent cause of mortality accounting for 286/500 deaths. This would be largely unsurprising to families and professionals familiar with PWS. The higher mortality rate in males with PWS might be accounted by cardiovascular disease being more prevalent in the male population generally, however, part of this phenomenon may also be due to risky behaviour by men with respect to their eating behaviour.
In Group 2, the data also indicates that there is a significant component of the causes of mortality that is linked directly to the behaviour of hyperphagia itself, rather than necessarily through the effects of obesity. This includes choking, respiratory infections, accidental poisoning, and water intoxication, all of which have been noted in several studies. There is also evidence of emergencies occurring due to binge eating, such as gastric rupture, with this being listed in one mortality study(Stevenson et al., 2007a) and a case report(Min et al., 2015).
In Group 3 there are a number of other factors that may contribute to an increased risk of death. Examples include: the severe leg oedema resulting in skin ulcers and impaired mobility and an increased risk of infection; dental decay secondary to sticky saliva and possible dental neglect that may increases the risk of choking; and excessive day time sleepiness secondary to sleep apnoea and the resultant risk of drowning, for example, in the bath. Severe kyphoscoliosis is also a reported problem in PWS, with affected individuals having reduced lung function. There are also reports of accidental deaths. The reasons for these are uncertain but poor judgment, impulsive behaviours, and temper outbursts might contribute to such risk. In addition, as average life expectancy for those with the syndrome increases, so research is required into whether there is an age-related neurodegenerative component to the syndrome(Whittington et al., 2015). In Fig.

2 we have summarized these nuances and the features of PWS that predispose people with PWS to excess morbidity and mortality that are not necessarily related to hyperphagia or its outcomes, but appear to feature as part of the syndrome.

With respect to interventions two key issues emerge: first, the importance of prevention, and, secondly, prevention is at present still about understanding the syndrome and managing the consequences. This specifically relates to hyperphagia and an appreciation that this inability to regulate food intake is part of a broad problem of impaired homeostatic regulation, which has a biological origin. These observations raise important questions for the support of people with PWS as to their ability make choices that can balance the various risks associated with excess food intake and to act accordingly, particularly in the context of the freedoms we have as adults and the ready availability of food in many countries. We have summarized the various management strategies including medical, surgical and social in Table 4 and note the variety of interventions that appear in the literature. However, although there are trials in progress, there are no treatments at present that have been shown to reduce the hunger drive and increase satiety at meal times to the extent that the treatment enables the person with PWS to regulate their own energy balance in an environment where food is freely available. Furthermore, none of these pharmacological treatments tested in adults are indicated in paediatric ages, which is often when obesity first develops. Growth hormone supplementation improves growth and muscle mass but it does not reduce hyperphagia. The clinical symptom of hyperphagia is part of a broader neuropsychiatric phenotype PWS, including obsessive compulsive behaviours, skin picking and emotional outbursts. Treatment strategies for these may include psychotropic medications (Bonnot et al., 2016). However the use of such medication remains contentious and is a poorly researched area and such treatments may increase the drive to eat and therefore the risk of obesity.

In the absence of effective and approved medical treatments for the hyperphagia, calorie control through the presence of a restricted food environment remains the mainstay of PWS treatment and management worldwide, alongside regular exercise. The presence of such an informed support environment can clearly prevent obesity but there are also potential risks with this mainstay of PWS management. Several papers in the literature highlight the risk of insufficient nutrient intake when following an over-zealous calorie limited diet plan(Mackenzie et al., 2018). The development and maintenance of a food secure environment therefore requires expert dietary advice ensuring, particularly during childhood, the right level of nutrient intake matched against the needs of growth and daily energy expenditure, and in the knowledge of the atypical

body composition and daily energy demands of people with PWS. In addition, support at meals is not only important to reduce the risk of obesity but also to reduce the risks of causes of mortality that are hyperphagia related but not directly due to obesity, such as choking.

6. Limitations

We note there are several likely biases that arise from a systematic review of this type, given that it is dependent on the published literature and may be biased towards countries with more developed healthcare systems. Our review has also only taken into account literature published in English, which is limiting for a genetic illness that is present worldwide.

7. Conclusions

Where early diagnosis, paediatric support, and information on PWS is available, parents can be expected to act in the best interests of their child with PWS and this means carefully managing the food environment. This review shows that not to do so will result in serious health risks. Where early diagnosis and information about PWS is not available then severe and life-threatening obesity is highly likely. With increasing independence in later childhood and adult life, maintaining such a food secure environment can be a major challenge. Balancing individual rights together with the prevention of harm makes the support of individuals with PWS a complex task for parents and carers to navigate.

Authors' contributions

SB, SA and LM reviewed the papers. SB also undertook the main drafting of the paper. IK developed the search strategies and undertook the searches and identified the papers. AH instigated and supervised the project and contributed to the writing and revisions of the review.

Declaration of competing interest

Anthony Holland is President of the International Prader-Willi Syndrome Organisation (IPWSO), a UK-based charity that supports people with PWS across the world. IPWSO instigated the project but had no role in the undertaking of the review, in the preparation of the manuscript, or in the interpretation of the findings. They did not provide any financial support. The other authors have no conflict of interest.

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