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# Contributing Factors of Mortality in Prader-Willi Syndrome

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## Abstract

Prader-Willi syndrome (PWS) is a multi-system disorder resulting from a lack of paternal gene expression in the 15q11.2-q13 region. Using databases compiled through response questionnaires completed by families known to the Prader-Willi Syndrome Association (USA), this study tested the hypothesis that PWS genetic subtype, BMI, age of diagnosis, clinical symptoms, and growth hormone treatment differ among deceased and living individuals with PWS. Categorical and continuous variables were compared using chi-square and two-group t-tests, respectively. Deceased individuals had higher rates of clinical features, including increased weight related concerns, heart problems, sleep apnea, other respiratory complications, diabetes, osteoporosis, high pain tolerance, and severe skin picking, when compared to living individuals. Meanwhile, living individuals had higher rates of growth hormone use and early puberty. Obesity and subsequent consequences are the primary contributors to increased mortality in PWS. Additional emphasis on areas to decrease mortality is needed.

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**Keywords**

Mortality; Prader-Willi syndrome; Obesity; Cardiac and respiratory failure; Growth hormone

## INTRODUCTION

Prader-Willi syndrome (PWS) is a multisystem disorder that is estimated to occur in 1/10,000 – 1/29,000 people (Cassidy, Schwartz, Miller, & Driscoll, 2011; Yearwood, McCulloch, Tucker, & Riley, 2011). PWS is initially characterized by neonatal hypotonia with poor suck and failure to thrive. Hyperphagia presents in early childhood and can gradually lead to morbid obesity if diet is not controlled. Additional features include typical cranio-facial features with cognitive, behavioral, neurological, endocrine, and psychiatric disturbances (Cassidy et al., 2011).

PWS is a disorder due to three different genetic mechanisms: a paternal chromosome 15q deletion, maternal uniparental disomy 15 (UPD), and microdeletion or epigenetic abnormalities of the imprinting center (Ledbetter et al., 1981; Nicholls, Knoll, Butler, Karam, & Lalande, 1989; Buiting et., 2003; Robinson et al., 1991). While all involve loss or absence of paternal gene expression in the 15q11.2-q13 region, clinical differences are reported among the different genetic mechanisms (Butler, 1990; Butler, Bittel, Kibiryeva, Talebizadeh, & Thompson, 2004; Cassidy et al., 1997; Gunay-Aygun, Heeger, Schwartz, & Cassidy, 1997; Roof et al., 2000; Holland et al., 2002; Veltman, Marijcke, Craig, & Bolton, 2005; Zarcone et al., 2007).

An increased overall death rate in PWS is present compared to the general population (Whittington et al., 2001; Vogels et al., 2003). One study reported that the mortality rate for the PWS population increases to 7% per year for those above the age of 30 years old compared to 3% across the age range of 0 to 47 years old (Whittington et al., 2001). Disease specific features appear to drive the PWS population's mortality rate, as PWS is a more substantial risk factor for death than intellectual disability alone (Einfeld et al., 2006). In addition, previous studies indicate that individuals who died had higher rates of UPD than those with a paternal 15q11-q13 interstitial deletion (Smith, Loughnan, & Steinbeck, 2003).

Causes of death are reported for both children and adults diagnosed with PWS (Butler, Manzardo, Heinemann, Loker, & Loker, 2017). Respiratory illness and sudden death associated with dysregulation of temperature are noted causes of death in infants and children while obesity related complications, including cardiovascular problems, diabetes, hypertension, and sleep apnea, are noted in adults with PWS (Schrander-Stumpel et al., 2004; Vogels et al., 2003; Tauber, Diene, Molinas, & Hébert, 2008). Recent research has shown that survival estimates for individuals with PWS have increased since 2000, especially with regard to cardiac deaths in females as well as thrombotic and gastrointestinal-related mortality (Manzardo, Loker, Heinemann, Loker, & Butler, 2017). The increase in survival in PWS may be attributed to earlier diagnosis and preventative measures to avoid morbid obesity (Manzardo, Loker, Heinemann, Loker, & Butler, 2017).

This study will test the hypothesis that PWS genetic subtypes, BMI, age of diagnosis, clinical symptoms, and growth hormone treatment will differ among deceased individuals and living individuals with PWS. This study will aim to identify the clinical characteristics amongst individuals with premature death reported to the Prader-Willi Syndrome Association (USA).

## MATERIALS AND METHODS

### Editorial Policies and Ethical Considerations

This study was reviewed and classified as expedited research by the Institutional Review Board of the University of California, Irvine (HS# 2014-–-1496). Consent was obtained from parents and caregivers of all patients.

### Study Design

This study relied on data collected from two questionnaires which were developed in conjunction with expert opinion from PWS physician experts (e.g. medical geneticists, endocrinologists, cardiologist), parent advocates, and staff of the Prader-Willi Syndrome Association (USA) [PWSA (USA)].

**Data on Living Individuals Diagnosed with Prader Willi Syndrome—**On October 10, 2004, a survey on patient prenatal, medical, and family histories was created by PWSA (USA) and posted on the organization's website. Families with an individual with PWS who are members of the PWSA (USA) were invited to participate in the survey. This survey could be printed out, completed, and mailed to the PWSA (USA) or submitted online. As of March 2014, about 1,961 families with an individual with PWS responded to this survey, referred to as Questionnaire 1 (see Supplemental Questionnaire 1). As PWSA (USA) was informed of the individual deaths, date of death, age, gender, and cause of death were noted. This left 1,915 living participants. Information collected from Questionnaire 1 included growth hormone treatment, BMI, the molecular basis for the diagnosis of PWS, and clinical symptoms.

**Data on Deceased Individuals Diagnosed with Prader Willi Syndrome—**In 2004, a familial-response questionnaire was created by the PWSA (USA) to collect demographic and cause of death on deceased individuals with PWS. This questionnaire was included in a supportive bereavement information packet that was sent at least twice in the first year following a death, and once in the second year. A letter of condolence and description of the process accompanied the questionnaire. Families were also given the option of having a physician from the PWSA (USA) committee call them to discuss the questionnaire by phone if there were questions filling out the form.

The bereavement program questionnaire form is referred to as Questionnaire 2. The request to complete this questionnaire was sent to all families who contacted the bereavement coordinator at PWSA (USA) (see Supplemental Questionnaire 2).

Information from Questionnaire 2 included whether participants received growth hormone treatment, BMI, molecular basis for the diagnosis of PWS, clinical symptoms, and

information specific to the deceased's cause of death. Institutional Review Board approval was previously obtained from the University of Utah. There were a total of 114 deceased individuals with PWS, 46 whose family members had completed Questionnaire 1 and 68 whose family members had completed Questionnaire 2.

### Data Analysis

This study compared previously collected data on deceased subjects with PWS and information on other subjects with PWS who were alive at last follow-up. Data were collected and archived by PWSA (USA) and made available for study. Outlier data were included, such as BMI that were not likely physically possible (e.g., BMI<14 and BMI>122). These data were not used in the analysis and constituted 5.6% of the overall data. Categorical variables (including PWS genetic subtype, clinical symptoms, growth hormone treatment) were compared using chi-square tests. Continuous variables (including age at diagnosis and BMI) were compared using two-group t-tests or the equivalent nonparametric test, if data were not normally distributed. The mean current age of last follow-up for the living population was younger than the mean age of death for the deceased population. It was therefore necessary to explore the effect of age as a confounding variable. The effect of age was limited with logistic regression. The IBM SPSS Statistics 21 was used for the data analysis.

Power analysis demonstrated 80% power to detect a difference between means of continuously distributed variables of 0.34 SD using a two-group two-sided t-test with 0.05 significance level with the expected sample size of 2,029 individuals. Power was estimated at >80% to detect a difference between proportions 0.12 to 0.18 using a two-group continuity-corrected chi- square test with a 0.05 significance level, assuming the expected proportion in the deceased group of 0.2 to 0.5.

## RESULTS

The total number of individuals with PWS included in this study was 2,029, including 114 deceased individuals and 1,915 living individuals. There was no significant difference between the living and deceased populations in relation to sex (see Table I). Furthermore, all regions of the United States were represented in the sample: 27.5% (539) were from the South, 25.3% (496) were from the Midwest, 21.0% were from the West (411), 18.1% (355) were from the Northeast, and 8.2% (160) were unknown. The self-reported PWS genetic subtype of the study participants is as follows: 41.9% (850) deletion, 19.2% (390) maternal UPD, 2.1% (42) imprinting defect, and 36.8% (747) unknown/other.

In this report, we describe the percentage of clinical symptoms in patients with PWS who either responded to the study questionnaire or had family members that responded on their behalf (see Table II). While other studies have analyzed the percentage of several of these factors, they were limited by small sample sizes. The overall percentage for clinical features including number of patients with deletion and maternal UPD, diabetes, scoliosis, osteoporosis, seizures, fractures, and eye abnormalities were compared to the percentage seen in previous studies (Laurier et al., 2014; Sinnema et al., 2011; Laurance, Brito, &

Wilkinson, 1981; Greenswag, 1987; Butler et al., 2002; Vogels & Fryns, 2003; Thomson, Glasson, & Bittles, 2006).

## Comparison by Living Status

The mean current age in living individuals with PWS was 22.4 years (range 2–84 years, SD=13.0) and the mean age at death for deceased individuals with PWS was 31.6 years (range 1–59 years, SD=14.5). This was significantly different (p<0.001) (see Table III). The median age was 32.0 years for deceased individuals and 19.0 years for living individuals. The average age at diagnosis for living and deceased persons was 3.8 (SD=12.7) and 7.4 (SD=9.8) years, respectively (p=0.078) (see Table III).

The current BMI in living individuals with PWS and the BMI level at their greatest weight in deceased individuals with PWS were 28.6 (SD=11.9) and 51.7 (SD=21.7), respectively and differed significantly (p<0.001) (see Table III). After adjusting for age the results of the logistic regression showed that BMI increases the likelihood that the patient was deceased by 7.3% for every unit of BMI (OR = 1.073).

For those individuals with PWS due to a paternal deletion or maternal UPD, 68.5% of living individuals had a deletion and 31.5% had UPD. Similarly, 68.6% of deceased individuals had a deletion and 31.4% had UPD. There was no statistically significant difference between living status and molecular subtype (paternal deletion and maternal UPD) (p=0.990) (see Table III).

Deceased and living individuals with PWS did not differ significantly with respect to hormone replacement therapy (e.g., estrogen/testosterone). The two populations also did not differ with frequency of assisted reproductive techniques, identical or fraternal twins, premature birth, breech delivery, tube feedings, or use of routine chromosome analysis (see Table III). There was also no significant difference with respect to curvature of the spine (scoliosis, kyphosis), bone fractures or other bone problems, hip dysplasia, eye problems, hypothyroidism, aspiration events, gastro/intestinal disorders, mitochondrial disorders, autistic behavior, or seizures (see Table IV). After adjusting for age as a continuous variable in logistic regression, several additional factors were no longer significantly different between the living and deceased PWS populations, including medication use (p = 0.051), emergency C-section births (p = 0.123), method of diagnosis (p = 0.749), use of FISH (p = 0.122), use of molecular/DNA testing (e.g. methylation) (p = 0.327), and gallbladder disease (p = 0.126).

There were several differences between the living and deceased populations, however, after adjusting for age with logistical regression. Living individuals were 3.06 times more likely to be taking growth hormone treatment (OR = 0.327) and 2.09 times more likely to have experienced early puberty (OR = 0.478). Deceased individuals were 8.6 times more likely to have weight concerns (OR = 8.576), 3.3 times more likely to have diabetes (OR = 3.300), 3.4 times more likely to have other respiratory complications (OR = 3.355), 2.9 times more likely to have heart problems (OR = 2.935), 2.7 times more likely to have severe skin picking (OR = 2.720), 3.0 times more likely to have high pain tolerance (OR = 2.965), 2.3

times more likely to have osteoporosis (OR = 2.254), and 2.6 times more likely to have sleep apnea (OR = 2.562).

### Phenotypic Details of the Deceased Population

The average age at death was 31.6 years (SD=14.5), with the oldest individual with PWS dying at 59 years of age and the youngest dying at 1 year of age. Caregivers reported that the deaths were "sudden" in 72.1% of the deaths and "unexpected" in 77.9%. The majority of deaths occurred in the hospital (52.9%) though several occurred at home (25.0%).

New physical symptoms were seen in 67.6% of the individuals before death (see Table V). New physical symptoms included shortness of breath in 18 individuals (39.1%) and swelling in 14 individuals (30.4%). Fourteen individuals (30.4%) also had a change of appetite with 10 reporting a loss of appetite (71.4%) and one reporting increased appetite (7.1%). Two additional individuals were reported to have weight loss in the weeks prior to death and one individual had weight gain. Abdominal pain was reported for 7 individuals (15.2%). An infection or virus was present in 7 individuals (15.2%). Other reported physical symptoms included fever (2 individuals), diarrhea (2 individuals), vomiting (2 individuals), incontinence (2 individuals), chest pain and/or atrial fibrillation (3 individuals), gallstones (1 individual), kidney complications (2 individuals), and "trembles" from seizures (1 individual). While a majority of the patients had new physical symptoms prior to death, only 26.5% had new complaints before death (see Table V).

In addition, 41.2% displayed behavioral changes prior to death (see Table V). Behavioral changes included fatigue/lethargy in 12 individuals (26.1%). Five individuals were noted to be more subdued while two were described as more aggressive prior to death. There was also a report of an individual who was more irrational, an individual who was confused, and individual who was restless, and an individual who was more irritable prior to death. Three individuals were also noted to have improved behavior such as listening to instructions more.

In this cohort, 86.8% and 89.7% of the patients had histories of feeding problems and hypotonia as infants, respectively. Snoring was present in 67.6% of the patients and 52.9% were reported to have thick saliva. Additionally, 88.2% had small hands and feet and 55.9% had vision problems, including nystagmus, vision loss, strabismus, and the need for glasses. One-fourth of patients had a history of choking episodes and 5.9% required the Heimlich maneuver. It was reported that 66.2% of patients with PWS vomited less than other individuals with the same type of illness. Finally, one-half of the individuals with PWS had problems with temperature control (see Table V). These clinical symptoms were not compared to living individuals, as it was not collected in Questionnaire 1 and therefore not available for review and analysis.

## DISCUSSION

A likely significant overlapping portion of this study's population was previously analyzed by Butler, Manzardo, Heinemann, Loker, & Loker (2017) and the causes of death in PWS by category (e.g., cardiac disease, infection, etc.) were reported. That report showed that 70%

of the deaths in patients with Prader-Willi syndrome occurred in adulthood with respiratory failure as the most common cause of death. Furthermore, males had an increased risk for presumed hyperphagia-related accidents/injuries as well as cardiopulmonary factors when compared to females. Finally, individuals with the maternal disomy 15 subtype had an increased risk of death from cardiopulmonary factors when compared to individuals with the deletion subtype.

This study adds further evidence to the hypothesis that obesity and obesity-related issues, such as diabetes, cardiac problems, and respiratory failure, are contributing causes of death in PWS as increased weight related concerns, heart problems, other respiratory complications, and diabetes were all more prevalent in the deceased PWS population. Deceased individuals with PWS were also more likely to have increased BMI, sleep apnea, severe skin picking, osteoporosis, and high pain tolerance when compared with living individuals with PWS. While living individuals had higher rates of early puberty than deceased individuals, they did not have higher rates of any other clinical symptoms tested compared to deceased individuals.

As obesity and its comorbidities are leading causes of death for individuals with PWS, historically external control of dietary intake and food security are necessary to combat the hyperphagia that classically accompanies a diagnosis of PWS, beginning in early childhood. Weight gain should be restricted by monitoring and adjusting daily food intake based on height, weight, and BMI. Establishing a food schedule as well as teaching children early that a parent or caregiver will closely monitor food intake and security to aid in food management. Accessibility to food may also be secured by controlling access to the refrigerator, freezer, and pantry as well as vending machines and access to money to purchase food (Forster & Gourash, 2005).

The role of growth hormone treatment must also be considered when caring for patients with PWS beginning as soon as the diagnosis of PWS is established genetically. Many of the symptoms that were more prevalent in the deceased population are reported to be influenced by growth hormone treatment. Growth hormone use has been shown to reduce body fat and improve muscle strength (Carrel, Myers, Whitman, Eickhoff, & Allen, 2010). In addition, improvements are noted in PWS including height, BMI, body composition, osteoporosis, improved gross motor skills, language acquisition, and cognitive scores (Eiholzer, Schlumpf, Nordmann, and L'Allemand, 2001; Eiholzer et al., 2004; Whitman et al., 2004; Festen et al., 2008; de Lind van Wijngaarden et al., 2009; Nyunt et al., 2009; Carrel et al., 2010; Colmenares et al., 2011; Khare et al., 2014). These data provide evidence of a potential link between the overlap of symptoms which were increased in deceased individuals with PWS and those influenced by growth hormone.

In support of this theory, deceased individuals were found to have lower rates of growth hormone use than living individuals even after adjusting for age. Similarly, recent research found a significant increase in survival for individuals since the FDA approved growth hormone treatment for individuals with PWS in 2000 (Manzardo et al., 2017). By decreasing the factors contributing to death such as weight gain, diabetes, and other obesity-related health complications, growth hormone treatment might decrease mortality.

This study also illustrates the potential importance of early diagnosis and careful surveillance. Although not statistically significant, deceased individuals were diagnosed at an older age (7.4 years) when compared to living individuals (3.8 years). In addition, growth hormone treatment has been shown to have a greater impact when started early (Carrel et al., 2004; Festen et al., 2008). Later diagnosis may explain why the deceased individuals had lower rates of growth hormone use. By delaying diagnosis, individuals may receive suboptimal treatment leading to greater morbidity. Diagnosing patients early can allow for growth hormone treatment implementation, therapies, and specific management, giving the patient the best possible prognosis.

Additionally, families and caretakers should have a low threshold for bringing their affected individual with PWS to medical attention when there is a concern. The majority of deaths were both unexpected and sudden. In addition, few affected individuals had new complaints or behavioral changes prior to their death. As a result, it is important that families are educated on factors surrounding mortality as well as the high pain tolerance within the PWS population.

Of note, no significant difference was found between PWS genetic subtype and living status as has been suggested by other studies. Further research is needed to investigate the subtle nuances of genetic subtype in the cause of death in PWS.

While this study contained a large cohort of individuals with PWS, it may not represent the total PWS population in the United States. This study includes individuals with PWS recruited primarily through the PWSA (USA) and therefore may have applied to only one specific patient population.

In addition to reported known mechanism of disease (e.g. deletion, maternal UPD, imprinting defect, and translocation), this study also included patients whose molecular subtype was unknown. Of this study's 2,029 participants, 36.82% (747) had an unknown molecular etiology. As a result, individuals who do not have a molecular diagnosis of PWS may have been included in this study. This may lend itself to results that are not completely reflective of the PWS population.

PWS patients and their families provided all of the data collected for this study through Questionnaires 1 and 2. The self-reported questionnaire answers were not confirmed by physicians, medical records, consult notes, or genetic test results. This study recognizes that self-reports without verification from medical records weakened the data collection from the PWSA (USA). Furthermore, while the questions were compiled based on a review of expert opinion from PWS experts, the questionnaires used to collect data for this study are not known validated questionnaires.

Additionally, there may have been some ambiguities with the surveys that led to inaccurate data collection. For example, patients with PWS and their families may have returned completed surveys with blank or inaccurate answers because they misunderstood the questions due to undefined medical terminology, such as FISH or "other respiratory complications." Families may also not have had the medical knowledge or familiarity with the affected relative to accurately answer all questions. As a result, clinical symptoms may

have been under-reported and responses for free response questions such as changes in physical symptoms prior to death may have been incorrect or non-contributory.

There is also the possibility that symptoms for deceased patients were over-reported compared to living patients due to biased recall. The majority of the data used for the deceased population came from the bereavement study with Questionnaire 2. Individuals and families who volunteer data for the bereavement study may differ from those who volunteer to participate in the PWSA (USA) survey. As a result, there is a possibility that the deceased individuals are not representative of the collective population of individuals with PWS whom are deceased.

While age was adjusted using logistic regression, it is possible that there may be residual confounding effects due to age differences that explains some of the associations. Further research will need to confirm these associations.

Finally, data used to compare BMI for the deceased population was reflective of the patient's greatest weight throughout their lifetime while data used for the living population was reflective of the patient's current weight at the time the survey was completed. This was done because the greatest weight of the living population was not collected. As a result, the difference in BMI between the living and the deceased populations may be overestimated.

Nevertheless, this study presents the comparison of a large cohort of living and deceased individuals with PWS and adds to the current literature surrounding mortality within PWS. It highlights the likely benefits of growth hormone treatment, external control of weight, early diagnosis, and the need for a low threshold for bringing affected individuals to medical attention. Using these measures, family members, care providers, and medical professionals can improve the longevity and quality of life for individuals with PWS.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGEMENT

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**Table I:**

Gender of Individuals with PWS

| | Living Patients with PWS | | Deceased Patients with PWS | | Chi Square |
|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | p-value |
| | | | | | 0.321 |
| Female | 974 | 51.5 | 26 | 59.1 | |
| Male | 916 | 48.4 | 18 | 40.9 | |
| Total | 1890 | 100 | 44 | 100 | |

**Table II.**

Clinical Symptoms Compared by Different Studies

| Physical Health Problems | This Study | Greenswag [1987] | Laurier et al. [2014] | Butler et al. [2002] | Sinnema et al. [2011] | Vogels et al. [2003] | Thomson et al. [2006] | Laurance et al. [1981] |
|---|---|---|---|---|---|---|---|---|
| N | 2,029 | 232 | 154 | 108 | 102 | 54 | 46 | 24 |
| Age range | 0–84 | 16–64 | 16/54 | 0–46 | 18–66 | 0–49 | 0–48 | 15–41 |
| Deletion; Uniparental disomy | 850;390 | --- | 101;24 | --- | 55;44 | 40;11 | 17;4 | --- |
| Diabetes | 10.56% (207/1,961) | 19% (44/232) | 25.30% | 24% (14/58) | 17% (17/102) | 7% (2/29) | 13% (4/30) | 20% (4/20) |
| Scoliosis | 32.87% (667/2,029) | ±50% | 75.40% | 41% (23/56) | 56% (57/102) | 34% (10/29) | 37% (11/30) | 62% (15/24) |
| Osteoporosis | 9.27% (188/2,029) | --- | --- | 2% (1/58) | 16% (16/102) | 14% (4/29) | 3% (1/30) | --- |
| Seizures | 11.01% (216/1,961) | --- | 19.00% | 8% (9/56) | 11% (11/102) | --- | 28% | --- |
| Fractures | 13.16% (258/1,961) | --- | --- | 43% (25/58) | 45% (46/102) | --- | --- | --- |
| Eye abnormalities | 44.26% (898/2,029) | ±50% | ---- | 59% (32/54) | 86% (88/102) | 52% (15/29) | 74% | --- |

**Table III:**

Patient Demographics and Details by Living Status

| | Living | | | Deceased | | | T-Test |
|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | p-value |
| Age (years) | 1912 | 22.37 | 12.96 | 114 | 31.57 | 14.52 | <0.001 |
| Age at diagnosis (years) | 856 | 3.76 | 12.65 | 39 | 7.39 | 9.76 | 0.078 |
| BMI/BMI at greatest weight (kg/m$^2$) | 1552 | 28.61 | 11.93 | 91 | 51.67 | 21.72 | <0.001 |
| | Living | | | Deceased | | | Chi-Square |
| | N (%) | | | N (%) | | | p-value |
| **Molecular Subtype** | | | | | | | 0.990 |
| Paternal Deletion | 815 (68.5) | | | 35 (68.6) | | | |
| Maternal UPD | 374 (31.5) | | | 16 (31.4) | | | |
| **Medication Use** | | | | | | | 0.046 |
| YES | 958 (50.0) | | | 30 (65.2) | | | |
| NO | 443 (23.1) | | | 4 (8.7) | | | |
| Unknown | 514 (26.8) | | | 12 (26.1) | | | |
| **Growth Hormone Treatment** | | | | | | | <0.001 |
| YES | 982 (51.3) | | | 25 (21.9) | | | |
| NO | 714 (37.3) | | | 72 (63.2) | | | |
| Unknown | 219 (11.4) | | | 17 (14.9) | | | |
| **Hormone Replacement Therapy (e.g. estrogen/testosterone)** | | | | | | | 0.149 |
| YES | 238 (12.4) | | | 9 (19.6) | | | |
| NO | 1677 (87.6) | | | 37 (80.4) | | | |
| **Assistive Reproductive Technologies** | | | | | | | 0.638 |
| YES | 55 (2.9) | | | 0 (0.0) | | | |
| NO | 1860 (97.1) | | | 46 (100.0) | | | |
| **Identical Twins** | | | | | | | 1.00 |
| YES | 19 (1.0) | | | 0 (0.0) | | | |
| NO | 1896 (99.0) | | | 46 (100.0) | | | |
| **Fraternal Twins** | | | | | | | 1.00 |
| YES | 32 (1.7) | | | 0 (0.0) | | | |
| NO | 1883 (98.3) | | | 46 (100.0) | | | |
| **Premature Births** | | | | | | | 0.640 |
| YES | 474 (24.8) | | | 10 (21.7) | | | |
| NO | 1441 (75.2) | | | 36 (78.3) | | | |
| **Breech Births** | | | | | | | 0.648 |
| YES | 429 (22.4) | | | 9 (19.6) | | | |
| NO | 1486 (77.6) | | | 37 (80.4) | | | |
| **Cesarean Section Births** | | | | | | | 0.022 |

| | | | |
|---|---|---|---|
| YES | 545 (28.5) | 6 (13.0) | |
| NO | 1370 (71.5) | 40 (87.0) | |
| **Tube Feeding** | | | 0.448 |
| YES | 1024 (53.5) | 22 (47.8) | |
| NO | 891 (46.5) | 24 (52.2) | |
| **Method of Diagnosis** | | | 0.005 |
| Clinical symptoms | 388 (21.1) | 17 (37.0) | |
| Blood Testing | 1449 (78.9) | 27 (58.7) | |
| **Diagnosed by FISH** | | | 0.003 |
| YES | 831 (43.4) | 10 (21.7) | |
| NO | 1084 (56.6) | 36 (78.3) | |
| **Diagnosed by DNA/Molecular Testing** | | | 0.040 |
| YES | 557 (29.1) | 7 (15.2) | |
| NO | 1358 (70.9) | 39 (84.8) | |
| **Diagnosed by Chromosome Analysis** | | | 0.527 |
| YES | 839 (43.8) | 18 (39.1) | |
| NO | 1076 (56.2) | 28 (60.9) | |

**Table IV:**

Patient Clinical Symptoms by Living Status

| | Living | Deceased | Chi-Square |
|---|---|---|---|
| | **N (%)** | **N (%)** | **p-value** |
| **Sleep Apnea** | | | <0.001 |
| YES | 829 (43.3) | 76 (66.7) | |
| NO | 1086 (56.7) | 38 (33.3) | |
| **Early Puberty** | | | 0.016 |
| YES | 293 (15.3) | 8 (7.0) | |
| NO | 1622 (84.7) | 106 (93.0) | |
| **Skin Picking** | | | <0.001 |
| YES | 646 (33.7) | 74 (64.9) | |
| NO | 1269 (66.3) | 40 (35.1) | |
| **Osteoporosis** | | | <0.001 |
| YES | 158 (8.3) | 30 (26.3) | |
| NO | 1757 (91.7) | 84 (73.7) | |
| **Spine Curvature (Scoliosis/Kyphosis)** | | | 0.754 |
| YES | 628 (32.8) | 39 (34.2) | |
| NO | 1287 (67.2) | 75 (65.8) | |
| **Bone Fractures** | | | 0.392 |
| YES | 250 (13.1) | 8 (17.4) | |
| NO | 1663 (86.9) | 38 (82.6) | |
| **Hip Dysplasia** | | | 1.00 |
| YES | 139 (7.3) | 3 (6.5) | |
| NO | 1774 (92.7) | 43 (93.5) | |
| **Other Bone Problems (not including scoliosis, kyphosis, fractures, or hip dysplasia)** | | | 0.559 |
| YES | 133 (7.0) | 4 (8.7) | |
| NO | 1780 (93.0) | 42 (91.3) | |
| **High Pain Tolerance** | | | <0.001 |
| YES | 897 (46.9) | 79 (78.2) | |
| NO | 1017 (53.1) | 22 (21.8) | |
| **Eye Problems** | | | 0.064 |
| YES | 838 (43.8) | 60 (52.6) | |
| NO | 1077 (56.2) | 54 (47.4) | |
| **Weight Concerns** | | | <0.001 |
| YES | 1252 (65.4) | 44 (95.7) | |
| NO | 661 (34.6) | 2 (4.3) | |
| **Diabetes** | | | <0.001 |
| YES | 190 (9.9) | 16 (34.8) | |

| | Living | Deceased | Chi-Square |
|---|---|---|---|
| | N (%) | N (%) | p-value |
| NO | 1723 (90.1) | 30 (65.2) | |
| **Hypothyroidism** | | | 0.194 |
| YES | 177 (9.3) | 7 (15.2) | |
| NO | 1736 (90.7) | 39 (84.8) | |
| **Aspiration Events** | | | 0.051 |
| YES | 197 (10.3) | 9 (19.6) | |
| NO | 1716 (89.7) | 37 (80.4) | |
| **Respiratory Complications** | | | <0.001 |
| YES | 381 (19.9) | 20 (43.5) | |
| NO | 1532 (80.1) | 26 (56.5) | |
| **Heart Problems** | | | 0.001 |
| YES | 181 (9.5) | 12 (26.1) | |
| NO | 1732 (90.5) | 34 (73.9) | |
| **Gallbladder Disease** | | | 0.018 |
| YES | 61 (3.2) | 5 (10.9) | |
| NO | 1852 (96.8) | 41 (89.1) | |
| **Gastric/Intestinal Disorders** | | | 0.790 |
| YES | 225 (11.8) | 6 (13.0) | |
| NO | 1688 (88.2) | 40 (87.0) | |
| **Mitochondrial Disorders** | | | 1.00 |
| YES | 22 (1.2) | 0 (0.0) | |
| NO | 1891 (98.8) | 46 (100.0) | |
| **Autism** | | | 0.468 |
| YES | 281 (14.7) | 5 (10.9) | |
| NO | 1632 (85.3) | 41 (89.1) | |
| **Seizures** | | | 0.358 |
| YES | 209 (10.9) | 7 (15.2) | |
| NO | 1704 (89.1) | 39 (84.8) | |

**Table V:**

Details and Clinical Symptoms of Deceased Individuals with PWS

| | Frequency (%) | | | Frequency (%) |
|---|---|---|---|---|
| **Place of death** | | | **Vomit** | |
| HOME | 17 (25.0) | | LESS | 45 (66.2) |
| HOSPITAL | 36 (52.9) | | SAME | 7 (10.3) |
| ANOTHER PLACE | 13 (19.1) | | MORE | 2 (2.9) |
| UNKNOWN | 2 (2.9) | | UNKNOWN | 14 (20.6) |
| **Sudden Death** | | | **Choking Episode** | |
| YES | 49 (72.1) | | YES | 17 (25.0) |
| NO | 16 (23.5) | | NO | 44 (64.7) |
| UNKNOWN | 3 (4.4) | | UNKNOWN | 7 (10.3) |
| **Unexpected Death** | | | **Heimlich Maneuver Required** | |
| YES | 53 (77.9) | | YES | 4 (5.9) |
| NO | 12 (17.6) | | NO | 59 (86.8) |
| UNKNOWN | 3 (4.4) | | UNKNOWN | 5 (7.4) |
| **Physical Symptoms** | | | **Temperature Control Problems** | |
| YES | 46 (67.6) | | YES | 34 (50.0) |
| NO | 12 (17.6) | | NO | 24 (35.3) |
| UNKNOWN | 10 (14.7) | | UNKNOWN | 10 (14.7) |
| **Behavioral Changes** | | | **Genetics Evaluation** | |
| YES | 28 (41.2) | | YES | 33 (48.5) |
| NO | 24 (35.3) | | NO | 21 (30.9) |
| UNKNOWN | 16 (23.5) | | UNKNOWN | 14 (20.6) |
| **New Complaints** | | | **Hypotonia** | |
| YES | 18 (26.5) | | YES | 61 (89.7) |
| NO | 23 (33.8) | | NO | 7 (10.3) |
| UNKNOWN | 27 (39.7) | | | |
| **Feeding Problems** | | | **Small Hands/Feet** | |
| YES | 59 (86.8) | | YES | 60 (88.2) |
| NO | 9 (13.2) | | NO | 8 (11.8) |
| **Snoring** | | | **Thick Saliva** | |
| YES | 46 (67.6) | | YES | 36 (52.9) |
| NO | 22 (32.4) | | NO | 32 (47.1) |
| **Vision Problems** | | | | |
| YES | 38 (55.9) | | | |
| NO | 30 (44.1) | | | |