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Hypothalamic obesity: Four years of the International Registry of Hypothalamic Obesity Disorders

Susan R. Rose, MD¹, Vincent E. Horne, MD¹, Nathan Bingham, MD, PhD², Todd Jenkins, PhD, MPH³, Jennifer Black, MSSA, LSW³, and Thomas Inge, MD, PhD⁴

¹Divisions of Pediatric Endocrinology, Vanderbilt University, Memphis, Tennessee;

²Cincinnati Children's Hospital Medical Center & University of Cincinnati College of Medicine, Cincinnati, Ohio, Division of Endocrinology, Vanderbilt University, Memphis, Tennessee;

³Bariatric Surgery, Vanderbilt University, Memphis, Tennessee;

⁴Division of Pediatric Surgery, Children's Hospital Colorado, University of Colorado, Denver, Aurora, CO

Abstract

Objective: Hypothalamic obesity (HyOb) is a rare cause of rapid weight gain and early metabolic co-morbidities. Effective treatment strategies are limited. Registry collected participant data and compared treatment approaches.

Methods: International Registry of Hypothalamic Obesity Disorders (IRHOD) was created as registry portal to provide education. Data collected from initial four years were evaluated.

Results: 87 participants were included for analysis (median age, 27y, range 3–71y). 96.5 were obese and 3.5% were overweight at maximal weight. 75 had brain tumors (86%)--majority were craniopharyngiomas (72%). Non-tumor etiologies included congenital brain malformation (4.6%), traumatic brain injury (3.4%), and genetic anomaly (2.3%). 90% received obesity treatments including nutritional counseling (82%), pharmacotherapy (59%), bariatric surgery (8%), and vagal nerve stimulator (1%). 46% reported follow-up BMI results after obesity treatment. Surgery was most effective (median BMI decrease -8.2kg/m^2 , median interval 2.6y), with lifestyle intervention (BMI -3.4kg/m^2 , interval 1.2y) and pharmaceutical therapy (BMI -2.3kg/m^2 , interval 0.8y) less effective. 80% of participants remained obese.

Conclusions: IRHOD registry identified a large cohort with self-reported HyOb. Surgical therapy was most effective at weight reduction. Nutritional counseling and pharmacotherapy modestly improved BMI. Stepwise treatment strategy to HyOb (including nutritional, pharmacological, and surgical therapies in experienced center) may be most valuable.

Keywords

hypothalamic obesity; obesity; brain tumor; hypopituitarism

Correspondence: Susan R. Rose, MD, MLC 7012; 3333 Burnett Ave, Cincinnati, OH 45229, Mslrose4@gmail.com.

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Registry Name, URL: International Registry of Hypothalamic Obesity Disorders; <http://www.irhod.org>

Introduction:

Hypothalamic damage or injury can result in a severe and devastating form of obesity (hypothalamic obesity [HyOb]). The hypothalamus is an important brain center that integrates neuronal and hormonal signals that regulate energy balance (1). While HyOb most commonly occurs following surgical management for brain tumors such as craniopharyngioma, pre-surgical hypothalamic involvement is already an independent risk factor for HyOb (2). Other potential etiologies include inflammatory disorders, infectious etiologies, stroke, radiation therapy, or traumatic brain injury (1).

In addition, underlying genetic defects affecting hypothalamic function can result in HyOb. Genetic causes include monogenetic obesity syndromes and complex genetic syndromes such as Prader-Willi Syndrome (PWS) and Bardet-Biedl Syndromes (BBS), which may cause obesity by disrupting the normal homeostatic mechanisms regulating energy balance centered within the hypothalamus (1).

Hypothalamic obesity is often severe, rapid, and inadequately managed with conventional treatment such as caloric restriction and lifestyle modification. The weight gain has a significant negative impact on quality of life and increases the risk for early cardiovascular comorbidities and morbidity/mortality in patients if effective treatment is not undertaken (3). While early identification and initiation of preventive measures (caloric-dietary control and maintenance of exercise) are critical components of HyOb therapy, these interventions typically result in a modest slowing of weight gain velocity, even when provided by a multi-disciplinary care system with strict lifestyle and behavioral modifications (4). Pharmacologic options and bariatric surgery are potential additional treatments for HyOb.

Despite many potential treatment options, clinical management of HyOb remains difficult. Development of optimal treatment strategies for these patients may be facilitated by better HyOb patient characterization and enhanced understanding of factors contributing to the weight gain. To that end, a registry was designed to identify and collect data on participants who have HyOb to evaluate patient characteristics, identify underlying etiologies, and compare treatment effects in this population. This report characterizes the results from the initial four years of registry data collection.

Methods:

The International Registry of Hypothalamic Obesity Disorders was a web-based registry created to collect participant-reported characteristics of HyOb from individuals affected by this relatively rare disorder regardless of etiology. The registry contained patient and provider orientation to HyOb including a description of etiologies, information on professional societies and support groups, recruitment information for research studies, and applicable clinical interventions. The website also provided direct access to registry enrollment. Following online consent, participants or caregivers complete a research questionnaire that was stored within the data repository.

Data collected included basic demographic data; diagnosis and information regarding the cause of HyOb; height, weight, BMI, and age at diagnosis; maximal and current height and weight; and any obesity treatments. Other medical diagnoses including mood and neurocognitive abnormalities, hormonal deficiencies, seizure disorder, hypertension, insulin resistance, non-alcoholic fatty liver disease, dyslipidemia, and cardiac disease were also collected.

Data in this report represents information collected from the IRHOD registry starting in April 2012 through February 2016. All participants who completed the registry were included in this analysis. All data were de-identified prior to analysis.

Subjects were stratified by BMI status. Subjects under age 20 years were classified using BMI percentile for age and gender. For these participants, BMI <85th percentile was considered normal weight, 85 to 95th percentile was considered overweight, 95 to 99th percentile was considered obese, and >99th percentile was considered severely obese. Severe obesity was further classified based on the percentile above the 95th percentage line, calculated using reported CDC percentiles for age and gender. This method has previously been used for the assessment of BMI change in patients already in the severely obese range (5). Adults over 20 years were classified using standard BMI categories: normal BMI (<25 kg/m²), overweight (25–30 kg/m²), obesity (30–40 kg/m²), or severe obesity (>40 kg/m²). Participants who reported follow-up weight and BMI characteristics were also compared by therapeutic classifications.

The primary aim of this report was to describe the registry participants, therefore no formal statistical tests were conducted. Basic descriptive statistics were used to characterize registry participants: frequencies and percentages are presented for categorical variables; means and standard deviations or medians and intra-quartile ranges (IQR) are presented for continuous variables. SAS v9.4 was used for all analyses.

Results:

Participant characteristics

A total of 107 persons enrolled in the registry. For this report, two participants were excluded based on implausible date of birth or missing height and weight, 17 participants were excluded due to lack of data in all categories, and one participant was excluded for reporting familial obesity, rather than HyOb, as the underlying cause of weight gain. A total of 87 participants therefore constituted the analysis cohort (Table 1). The cohort was primarily female (69%) and Caucasian (90%). Median age at the time of analysis was 27 years (range 3 – 71 years), with 58% of subjects age 20 years or older. Median BMI for participants younger than age 20 years was 32.8 kg/m² (IQR 25th–75th, 29.4–39.1 kg/m²) with median BMI z-score of 2.53 (IQR, 2.22–2.72), while those 20 years or older had median BMI of 42.1 kg/m² (IQR, 35.7–52.3 kg/m²). Participants resided in multiple countries, with 76% of respondents reporting the United States as their country of origin.

A variety of etiologies causing HyOb were reported by the registry participants. Most commonly, 75 participants (86%) reported HyOb as a result of a brain tumor or tumor

therapies including surgery and radiation. In this cohort, most tumors were craniopharyngiomas (72% of all with brain tumor, 62% of the total registry), with the second most common being astrocytoma or macroadenoma of the pituitary, each occurring in 7% of respondents (Table 2). Craniopharyngioma was the single most common etiology across the cohort (62%). Congenital brain malformations (including congenital hypopituitarism, optic nerve hypoplasia, or congenital cavernous malformation) were identified as a cause of HyOb in 4.6% of respondents. Either hemorrhage or traumatic brain injury were identified as the cause of HyOb in 3.4% of respondents. Genetic causes of HyOb were identified in 2.3%, one participant with leptin deficiency and one with PWS. However, the participant with PWS also had a diagnosis of craniopharyngioma. Finally, 4.6% of respondents did not report a cause of their HyOb.

Many co-morbid conditions were reported by participants (Table 3). Pituitary dysfunction was the most common comorbidity, reported in 88.5% of respondents. Eighty-three percent reported multiple endocrinopathies, and 46% reported four or more deficiencies. Hypothyroidism was the most common deficiency (90%) followed by adrenocorticotrophic hormone (ACTH) deficiency (73%). However, other endocrinopathies were also common. Ten participants (11.5%) reported no endocrinopathies, and thus had isolated HyOb.

Neuropsychological co-morbidities (including seizures, psychiatric illness, or ADHD) were reported in a total of 9% of the participants. Metabolic abnormalities were infrequently reported. Although only 3% of subjects reported hyperinsulinemia, hyperglycemia, or treatment for diabetes mellitus; 31% of subjects reported use of metformin for weight loss therapy. However, given the limitation of self-reported data, it is unclear how many participants had insulin resistance or other metabolic derangements requiring treatment.

Obesity therapy

Ninety percent of participants reported having had some type of obesity treatment (Table 4). Interestingly, 10% did not report any therapy. Nutritional counseling was most commonly reported (82%). Counseling type varied, with 52% having dietician-supervised counseling, 41% having physician-only counseling, and 7% not specifying the method of nutritional counseling.

Pharmacotherapy was reported by 59% of participants (including 33% of those under 20y of age), with 25.5% report multi-drug therapy. Of the reported medications, metformin was the most commonly used medication, in 53% of participants. Stimulant therapy was the second most commonly used, with 49% using dextroamphetamine, methylphenidate, or ephedrine. Orlistat was the third most common therapy, used by 14% of respondents. Caffeine was used by 6% of respondents, and sibutramine was used by 4% of respondents. Octreotide and venlafaxine (serotonin reuptake inhibitor) were used by one participant each.

Additionally, 8% of participants underwent bariatric surgery for treatment of HyOb. Sleeve gastrectomy was the most common therapy (57%), followed by RYGB (28.5%), and laparoscopic banding in one patient (14%). One patient received vagal nerve stimulator (VNS) therapy in addition to bariatric surgery.

Weight effects

At maximal reported weight, 96.5 of respondents reported data consistent with obesity and 3.5% consistent with overweight. Seventy-two percent of respondents were classified with either childhood or adult definitions of severe obesity ($\geq 140\%$ of the 95thile, or class 3 obesity or BMI ≥ 40 , respectively). Twenty-five percent of respondents also reached extreme weight and BMI ranges, with 22% of adults having a BMI $>55 \text{ kg/m}^2$ and 30% of children having a BMI $>160^{\text{th}}$ percentile of the 95th percentile for age and gender, highlighting the more extreme impact of obesity in this cohort.

Only 46% of participants had reported follow up weight and height characteristics at the time of our analysis. There was a trend towards weight reduction in these participants (Figure 1). However, only one participant reached a normal weight, 18% remained overweight, and overall 80% remained in the obesity range with 55% of respondents continuing to have severe obesity.

Of the 40 participants that reported follow-up weight, effects of medical, surgical, or nutritional therapies were compared. Surgical therapy (6 reporting follow up) was the most effective at decreasing BMI with a median BMI decrease of 8.2 kg/m^2 with median follow up 2.6 years. Participants receiving medication therapy with lifestyle changes (21 reporting follow up) also had improved weight loss with a median BMI decrease of 2.3 kg/m^2 with median follow-up of 0.8 years. However, participants reporting only lifestyle counseling (11 reporting follow up) had a larger BMI loss than did the medical therapy group with a median BMI decrease of 3.4 kg/m^2 at median follow up of 1.2 years. Participants reporting any treatment for obesity had a median BMI decline of 2.6 kg/m^2 (median follow up 1.0 year). The participant who received vagal nerve stimulation implantation did not report follow-up weight.

Discussion:

The IRHOD registry is comprised of a large cohort of participants with diverse geographical and age characteristics who have hypothalamic obesity. Etiologies, treatment modalities, and treatment effects were reported in children and adults with this disorder. There are limited previous data comparing different treatment strategies available, due at least in part to the rarity of HyOb. The IRHOD database serves as a tool for compiling a large cohort of HyOb patient data.

Common clinical characteristics of HyOb were observed in most cohort participants, with the majority of participants having severe obesity, reporting brain tumor and tumor therapies resulting in HyOb, and with craniopharyngioma being the most common etiology overall. These data are consistent with previous reports, since craniopharyngiomas are located at the sellar/suprasellar region where the hypothalamus and structures involved in weight regulation are located (6–10). Tumors in this location often require extensive surgical resection with or without radiation therapy, leading to the rapid weight gain (6–8). However, hypothalamic-sparing surgical techniques have reduced the injury to central weight regulation pathways and thus reduced the risk of subsequent HyOb (9, 11).

Due to the underlying etiologies of either brain injury, congenital malformation, or associated genetic syndromes, most participants had the key feature of pituitary dysfunction resulting in endocrinopathies. Interestingly, hypothyroidism was the most common deficiency followed by adrenocorticotrophic hormone deficiency. Typically, these two deficiencies are considered to be the least common abnormalities in the general population of brain tumor survivors (12, 13). However, since the location of hypothalamic tumor in this population with HyOb is likely to involve critical areas for regulation of pituitary function, high rates of all endocrinopathies are expected.

Unfortunately, pharmacologic agents available for effective obesity treatment are limited, particularly in the pediatric age range (14, 15). In addition, many treatment studies for HyOb have been underpowered (16). Of note, pharmaceutical therapies targeting central pathways of appetite regulation may not be effective for HyOb, due to disruption of the hypothalamic pathways targeted by these agents. Therapies that target efferent pathways may be more efficacious. The primary mechanism stimulating appetite in HyOb has been loss of inhibition of insulin secretion (6).

Several of the most effective agents for weight loss have been withdrawn from the market, or have limited use due to concerning side-effect profiles. Sibutramine, a centrally-acting serotonin-norepinephrine reuptake inhibitor with some efficacy for weight loss, was withdrawn from the market due to increased risk of cardiovascular mortality and stroke (6, 17). Orlistat, a lipase inhibitor, is also an effective means of weight reduction, but often results in gastrointestinal effects that are not always tolerable (18, 19). Metformin has been effective in exogenous obesity by making tissue more sensitive to insulin, resulting in reduction of insulin secretion (20), thus may lack efficacy for the primary insulin excess in HyOb. Inhibitors of insulin secretion such as octreotide or diazoxide may reduce weight velocity in HyOb, but have serious side effect profiles (20, 21). Octreotide has been the most widely attempted therapy with reported benefit of weight stabilization, but involves frequent injections and has risk of gallbladder disease. (8, 11).

Stimulant therapies such as methylphenidate or dextroamphetamine have shown benefit by reducing the velocity of weight gain in patients with HyOb. These have been used in children for treatment of ADHD, and are overall well-tolerated (22, 23). Stimulants are an appealing therapy option due to the well-known effects of increased metabolic rate and reduced appetite as well as an acceptable safety profile, particularly in children as young as six years (22, 23). Several emerging treatment options have not been well described in children with HyOb, but may be effective in adults with HyOb. Glucagon-like peptide analogues caused weight reduction by potentiating insulin secretion and improving satiety in adults with HyOb, but may also have adverse side effects (24, 25).

Vagal nerve stimulation (VNS) has been proposed as a possible therapy for obesity and has been studied in participants with underlying psychiatric disorders (26). There are conflicting reports between existing studies - some report weight loss while others show limited weight changes (27–29). Overall effects on obesity may be related to reduced food cravings, a potential target for patients with HyOb (30).

In the IRHOD database, bariatric surgery was associated with the largest weight loss in the HyOb participants and arguably had the biggest metabolic effect. Sleeve gastrectomy was the most common surgical approach, RYGB was the second most common, and only one participant underwent gastric banding. Bariatric surgery has been a proposed treatment for HyOb even at pre-adolescent ages, given the inability for patients with HyOb to slow weight gain and with expected early metabolic comorbidities. Prior experience suggests that RYGB, compared to other surgical methods, may more potently counter the underlying biological predisposition to weight gain, through facilitating early and accentuated postprandial excursions of satiety-related hormones (31–34). Favorable outcomes included decreased food cravings and sustained weight loss in HyOb subjects (35). A systematic review of case series noted that with RYGB, a 17% reduction of BMI was sustained at two years after surgery (34). However, longer term data are needed to determine the lasting long-term effects of surgery on weight control. Surgical therapies should be considered for HyOb patients with extreme levels of obesity who are at risk of early elevation of co-morbidities and cardiovascular mortality. Of course, prior to procedures in the pediatric age group, informed parental consent and patient assent must be obtained, and it is important to discuss ethical concerns regarding non-reversible bariatric procedures in minors.

Lifestyle interventions were not universally provided, as only 52% of respondents reported receiving dietician counseling and the rest of the reported intervention came from physician-led counseling. It is possible that some participants did not identify that they were receiving counseling, or that they received parental counseling, or made self-motivated educational or dietary changes. It is possible that participants under-reported self-motivated lifestyle changes that would have an impact on weight outcomes. While physician-provided counseling is certainly an important aspect of HyOb treatment, involvement with registered dietitians is likely to provide advantages in achieving behavioral change. The addition of psychologist-assisted behavior modification may also improve weight outcomes in conjunction with dietician and physician-led management in some settings (4).

Despite lifestyle, medical, and surgical interventions, 80% of participants in the IRHOD registry remained obese, with 55% remaining severely obese. However, it is likely that their BMI reduction still would have a positive effect on metabolic outcomes resulting in improvement in mortality, co-morbidities, and quality of life (36). Of note, metabolic outcomes were not explicitly surveyed by the registry. Although an appreciable BMI reduction was evident over time in our registry, long-term risks of obesity and cardiovascular outcomes were not completely mitigated. The modest reduction of BMI in our cohort is consistent with historical difficulty in achieving long-term weight control in HyOb.

In this study lifestyle modification was as effective as pharmaceutical therapy combined with lifestyle changes in many subjects. This is surprising given the expectation that more intensive interventions would result in greater weight loss. However, confounding variables may affect this outcome, such as selection bias. It is possible that those patients who had the most refractory weight control were selected for pharmaceutical therapy. Caution should be applied with use of the medical therapies observed in this study and providers should expect only a modest change in overall BMI. Prior studies support BMI stability being the best achievable outcome with certain treatments. Stable BMI may be an important targeted

outcome in patients with HyOb who continue to have rapid weight gain despite lifestyle intervention. If weight stabilization is the goal, then early initiation of lifestyle and/or pharmaceutical intervention is indicated.

The fact that respondents did not report experience using newer pharmaceutical interventions is a limitation of this study. Glucagon-like-polypeptide-1 analogs that are now being prescribed may slow weight gain velocity and cause weight loss in some subjects (34). At least half of the subjects in the current study (53%) reported treatment with metformin for weight control, which may be used as therapy for exogenous obesity, particularly in combination with lifestyle modification to achieve weight loss (37). However, metformin has been hypothesized to be less effective in HyOb, as the mechanism of weight gain in patients with HyOb is primary excess of insulin, not insulin resistance (6). Minimal data on efficacy of metformin in HyOb subjects are available (21, 38). Therefore, weight loss may have been improved if other medications were used in lieu of metformin.

Other limitations to the study include the nature of a survey format for data, missing data from the database that required exclusion of some subjects, limited longitudinal data, and predominance of Caucasian adult females within the survey group. The conclusions and analysis are still generalizable to the overall HyOb population due to inclusion of a diverse participant population and the fact that HyOb does not have a known predominance in a particular population group. Due to insufficient numbers of respondents in the no treatment group, comparisons involving this group lack statistical significance. Differences in follow up time among the treatment groups also may affect outcomes and long-term effects in weight trajectories. Strengths of our study include the large number of subjects with this rare disorder, evaluation of different etiologies resulting in HyOb, comparison of different treatment modalities in HyOb subjects which have not previously been evaluated, and the relatively long follow-up time within the treatment groups.

Overall, children and adults who are diagnosed with brain tumors in the hypothalamic-pituitary location should be proactively counseled about the risk and seriousness of developing HyOb. Early recognition and aggressive management of HyOb is critical, and, as previously reported, early management can slow weight gain in order to prevent extreme levels of obesity. Lifestyle intervention with registered dietician counseling is an important first step of therapy. Pharmacotherapy could be considered as a next step, particularly in patients who are continuing to have unremitting weight gain despite counseling. If extreme obesity remains difficult to manage despite these therapies, bariatric surgery continues to be the therapy modality that can most rapidly reduce weight and BMI, thereby reducing risks of adverse cardiovascular outcomes in these patients.

Given the rarity of HyOb disorders, evaluation and management in a center with experience in treatment of HyOb should improve outcomes. This would include teams experienced in pharmacologic as well as surgical treatments. Many times, combination therapies are required. Further study is needed of the clinical outcomes of newer medical and surgical therapies, in order to better understand optimal treatment protocols for hypothalamic obesity.

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What is known about this subject?

- Hypothalamic obesity is a rare but significant form of obesity, resulting in rapid weight gain and early cardiovascular disease, particularly in brain tumor survivors
- Treatment strategies have had varying success, but a unified weight management strategy for hypothalamic obesity remains unclear
- Small populations within previous studies limit the ability to study hypothalamic obesity and weight outcomes following therapy

What does this study add?

- Using a web based portal, we have designed a registry to collect data about participants with hypothalamic obesity to be used for current and future study
- Using data from registry participants, we are able to describe characteristics, compare treatment approaches, and evaluate weight outcomes among the cohort retrospectively

Figure 1:
Comparison of BMI before and after weight loss intervention (n=40).

Table 1:

Participant Demographics (n=87)

Demographic	Total	Percent
Female gender	60	69%
Median Age (IQR 25–75)	27.8 years (15.2–42.1)	N/A
Age <20y (range 3.6–19.7y)	36	41.4%
Age >20y (range 21.9–71y)	51	58.6%
Race		
Caucasian	79	90.8%
Asian	3	3.4%
African Descent	3	3.4%
More than 1 race	2	2.3%
Country of Origin		
United States	66	75.9%
Australia	6	6.9%
United Kingdom	3	3.4%
Canada	2	2.3%
New Zealand	2	2.3%
Russia	1	1.15%
Netherlands	1	1.15%
China	1	1.15%
Uruguay	1	1.15%
No answer	4	4.6%

Table 2:

Tumor etiologies (n=75)

Tumor type	Total	Percent
Craniopharyngioma	54	72.0%
Pituitary macroadenoma	5	6.7%
Hamartoma	2	2.7%
Meningioma	2	2.7%
Juvenile pilocytic astrocytoma	2	2.7%
Langerhans cell histiocytosis	2	2.7%
Pilomyxoid astrocytoma	1	1.3%
Ganglioglioma	1	1.3%
Anaplastic astrocytoma	1	1.3%
Astrocytoma, not specified	1	1.3%
Glioma	1	1.3%
Unknown pathology	3	4.0%

Table 3:

Co-morbidities (n=87)

	Total	Percent
Psychiatric illness	5	5.7%
Seizures	3	3.4%
Hypertension	3	3.4%
Hyperglycemia / Diabetes	2	2.3%
Insulin resistance	1	1.1%
Pituitary Dysfunction	77	88.5%
Hypothyroidism	69	89.6%
ACTH deficiency	56	72.7%
GH deficiency	48	62.3%
Diabetes insipidus	38	49.3%
Hypogonadism	36	46.7%
Total Number of Endocrinopathies	77	
1	13	16.9%
2	13	16.9%
3	15	19.5%
4	17	22.1%
5	19	24.7%

Table 4:

Treatment options (n=87)

	Total	Percent
Nutrition counseling	71	81.6%
Pharmaceutical therapy	51	58.6%
Bariatric surgery	7	8.0%
Vagal nerve stimulator	1	1.1%
No treatment reported	9	10.3%
Medication therapy		
Metformin	27	52.9%
Dextroamphetamine	12	23.5%
Ritalin	8	15.7%
Orlistat	7	13.7%
Ephedrine	5	9.8%
Caffeine	3	5.9%
Sibutramine	2	3.9%
Octreotide	1	2.0%
Venlafaxine	1	2.0%
Surgical therapy		
Sleeve gastrectomy	4	57.1%
Roux-en-Y gastric bypass	2	28.6%
Laparoscopic band	1	14.3%
Nutritional counseling		
Dietician supervised	37	52.1%
Physician supervised	29	40.8%