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Health outcomes of children with Prader-Willi or Angelman Syndromes: a European population-based multi-centre study

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ABSTRACT

Background/Aim. Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are rare imprinting disorders caused by the aberrant expression of 15q11.2-q13 imprinted genes. Due to their rarity, data on health outcomes during infancy are limited. This EUROlinkCAT study aimed to investigate major health outcomes of children with these chromosomal disorders.

Methods. Data of children born in 1995-2014 and diagnosed with PWS (n=150) or AS (n=46), collected by 11 population-based congenital anomaly registries, were linked to local electronic healthcare and mortality databases and analysed.

Results. Children with PWS had a survival rate of 94% (95% CI 89.5-98.7%) by 10 years of age. Nearly all children (99.5%, 95% CI 97.6-99.9%) with PWS required hospitalization during the first year of life with a median length of stay of 25 days; a high proportion continued to need hospital care later in life (93.2% at 1-4 years and 79.6% at 5-9 years) with shorter stays (1.2 and 0.5 days per year, respectively). In comparison, no deaths occurred among children with AS by 10 years of age. Fewer children with AS required hospitalization in the first year of life (59.0%, 95% CI 39.6-74.0%); as they grew older, the proportion admitted was 68% (95% CI 40.0-85.0%) at 5-9 years. Children with PWS and AS underwent first surgery at approximately 1.8 years and 2.5 years, respectively.

Conclusions. This study provides valuable evidence for improving family counselling and promoting an adequate healthcare support system.

Abstract: 237 words

Key messages:

- Existing literature on Prader-Willi syndrome (PWS) and Angelman syndrome (AS) only addressed specific aspect of these diseases, involved small case series or reported on broad age-cohorts.
- This population-based cohort study aimed to investigate the health outcomes of European children born with PWS and AS by analysing data from 11 EUROCAT registries covering 5.6 million births from 1995 to 2014 and including 150 children with PWS and 46 children with AS.
- The study provided previously unavailable estimates of survival rates, hospitalizations and number of surgeries in children with PWS and AS, offering critical data for counselling parents and informing clinicians.

Statements and Declarations

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Competing interests

The authors declare no competing interests to disclose.

Author contributions

MVA designed the study, developed statistical analysis plan, performed the analysis, interpreted the results, drafted the initial manuscript, and reviewed and revised the manuscript. IB conceptualized and designed the study, interpreted the results, drafted the initial manuscript, and reviewed and revised the manuscript. MS and AC conceptualized and designed the study, developed statistical analysis plan, contributed to the data analysis and interpretation of the results, and critically reviewed the manuscript for important intellectual content. JT contributed to development of study methods, including data standardization and data linkage, development of statistical analysis plan, writing analysis programs, data analysis and interpretation of the results, and critically reviewed the manuscript for important intellectual content. EG contributed to

obtaining funding, development of study methods, including data standardization and data linkage, to interpretation of the results, and critically reviewed the manuscript for important intellectual content. ML contributed to obtaining funding, development of study methods, was responsible for data standardization and management of data linkage by the participating data providers, contributed to data analysis and interpretation of the results, and critically reviewed the manuscript for important intellectual content. LO contributed to design the study, interpreted the results and critically reviewed the manuscript for important intellectual content. EB, CC, MGa, MGi, SJ, KK, IM, and DW were responsible for data linkage and standardization for their registries' data and running centrally written syntax scripts for local analyses, and critically reviewed the manuscript for important intellectual content. JM conceptualized and designed the study, obtained funding, developed study methods, including data standardization and linkage, supervised writing analysis programs, performed statistical analysis, supervised the work, and reviewed and revised the manuscript.

Joan K. Morris is the guarantor.

All authors approved the final manuscript as submitted and agree to be accountable for major aspects of the work.

Data availability

Aggregate data supporting the findings of this study are available from the participating registries of congenital anomalies (CAs). Data were used under license for the current study. Because restrictions apply to the availability of these data, no publicly available data are present. However, data can be released from the authors for scientifically valid requests, upon permission of the participating registries of CAs.

INTRODUCTION

Prader-Willi syndrome (PWS) (MIM #176270) and Angelman syndrome (AS) (MIM #105830) are classified as imprinting disorders. Although less than 1% of all genes are imprinted, imprinting disorders constitute a significant proportion of genetic diseases.

PWS and AS are chromosomal disorders characterized by altered expression of genes mapped on the 15q11-q13 chromosomal region due to genomic imprinting. Although sharing a common genetic cause, they exhibit substantially different phenotypic and clinical features.

Prader-Willi syndrome

PWS has a birth prevalence of 1 in 10,000-30,000 [1] and it affects males and females and those from different ethnicities equally [2]. PWS is the consequence of the loss of paternally active genes of the 15q11.2-q13 region. PWS is not generally an inherited disease, it rather occurs as sporadic genetic abnormality taking place during gametogenesis or embryonic development [3].

Clinical manifestation of PWS is unorthodox as it radically changes over time. In neonates with PWS, a primary sign of the disorder is poor muscle tone accompanied by reduced responsiveness to stimuli and weak cry. Due to hypotonia, neonates manifest poor sucking and challenging feeding, which leads to poor weight gain, sometimes necessitating the use of tube feeding for about 3 to 4 months [4]. As babies with PWS grow, both muscle tone and feeding abilities improve. However, as they enter into early childhood they start over-eating (hyperphagia) and exhibit frequent food-seeking behaviours due to the lack of satiety cues [5]. In the absence of proper management, this can result in morbid obesity. The management involves multiple medical specialists to mitigate disorder complications and greatly improve life expectancy and overall quality of life [6].

Angelman syndrome

The prevalence rate of Angelman syndrome is still a matter of debate: different studies show variability from 1 in 10,000 births to 1 in 56,000 births [7–11]. AS is caused by the loss of maternally active genes of the 15q11.2-q13 region. DNA methylation analyses of the 15q11.2-q13 chromosome region allow the detection of about 80% of all positive cases, including those deriving from a deletion, UPD or imprinting defect [12].

Infants with Angelman syndrome show severe developmental delay and intellectual disability, unstable gait, balance issues (ataxia) and feeding problems. Seizures usually begin between the age of 18 months to 3 years [12]. Additional phenotypic characteristics include microcephaly, severe speech impairment, sleep problems and easy excitability with frequent laughing [13].

Given the rarity of these two genetic syndromes, there is a lack of studies evaluating the health outcomes of children with PWS and AS. Most of the existing research typically addresses only specific aspects of the disease, involves small case series or reports on broad age cohorts [14–16]. Therefore, there is little population-based information on health outcomes of children born with PWS or AS. This study aimed to investigate the health outcomes of European children born with PWS and AS by assessing survival rates, hospitalization rates and the frequency of surgeries.

METHODS

This study is part of the EUROlinkCAT project, which sought to explore the health outcomes of children affected with major congenital anomalies (CAs) by linking population-based CA registries to electronic mortality and healthcare databases [17]. Data from 11 European Surveillance of Congenital Anomalies (EUROCAT) registries [18,19] in 7 European countries were included (Table 1). Children born between 1995 and 2014 with PWS were identified in the

EUROCAT registries by the following codes: ICD-10 BPA code Q8715, ICD-9 BPA code 759872, OMIM 176270, while children with AS were identified by ICD-10 BPA code Q8785, ICD-9 BPA code 759899, and OMIM 105830).

EUROCAT systematically collects data on congenital anomalies diagnosed prenatally or in infancy using multiple sources of ascertainment, as outlined in EUROCAT guidelines [20]. Congenital anomaly cases were recorded as follow: 6 registries (Emilia Romagna, Tuscany, Malta, Norway, Valencia region, UK-Wales) included cases up to 1 year of age; 1 registry (Finland) included cases up to 1 year of age for surveillance purposes, though later diagnoses were also recorded; 1 registry (Paris) included cases up to 1 week of age or later if discharged from maternity occurred afterwards; and 3 registries (UK: EM SY, Thames Valley and Wessex) had no upper age limit. Three registries (Finland, Paris and Malta) covered the whole study period, while four registries (Finland, Norway, Wales and Malta) encompassed the whole country. Data from participating registries were linked to their respective regional healthcare databases in order to collect information on mortality, hospitalization, and surgical procedures [17,21–25].

All live born children with no congenital anomalies, obtained from the same population covered by the registry and born in the same time period, were used as the reference population. Tuscany selected a 10% sample of their population, matched by date of birth and sex. No reference population was available for three English registries. Hospitalization and surgical procedures data were not available for Paris, Norway and Malta registries. Linked data were included up to the child's 10th birthday or to 31st December 2015, whichever came earlier [17]. Variation in time periods was the result of registries having different years of EUROCAT membership, with only those years showing high-quality healthcare data and a successful linkage rate being included [21]. Additional details of linkage methodology were previously published [17,21,22].

Hospitalization rates for children with PWS and AS, excluding hospital admission associated with the birth , were compared to those of the i) reference population and to those of ii) children born with any other major CA [26]. We excluded hospital admissions at age zero (day of birth) or age 1 day, where the only diagnosis was "obstetric".

Statistical analyses

Data analysis was performed locally by the registry using common STATA syntax scripts. Only aggregated data and analytic results were uploaded and shared with the Central Results Repository based at Ulster University (UK) via a secure web platform [17]. Each registry performed Kaplan-Meier survival analysis to account for censoring, due to loss of follow-up arising from emigration or not attaining the age of 10 by 31st December 2015. Survival estimates with 95% confidence intervals (CI) from each registry were combined in a random-effects meta-analysis to calculate pooled estimates, using a modified method published by Combescure et al. [27]. Survival rates were calculated at 1 week, 4 weeks, 5 and 10 years. Kaplan-Meier analyses were also used to estimate the percentage of children: hospitalized, hospitalized longer than 10 days for term-born infants, undergoing surgery. Overall estimates were calculated for age groups using a random effects meta-analysis. The median length of hospital stay (LOS) per year was calculated for each registry by scoring the number of days spent in the hospital between the date of admission and the date of discharge. Outpatient visits were excluded from LOS calculation. Random effects meta-analyses were then performed in R (version 4.0.3), using the "metamedian" package, for three age groups: < 1 year, 1-4 years, and 5-9 years. Pooled estimates of the median age at the first surgery and median number of surgical treatments were calculated for three age groups: < 1 year, 1-4 years and 0-4 years.

STROBE cohort-reporting guidelines have been applied to this paper [28].

Ethical approval

All EUROCAT registries data that contributed to the EUROlinkCAT project obtained ethical, governance and other permissions for data linkage, according to their national legislations and arrangements. The university of Ulster obtained Ethics permission for the Central Results Repository on 15 September 2017 (Institute of Nursing and Health Research Ethics Filter Committee, number FCNUR-17-000). Each registry uploaded aggregated data exclusively to the research team. Individual consent was not required since no individuals could be identified from the uploaded information.

RESULTS

Data from 11 EUROCAT registries covering 5.6 million births from 1995 to 2014 included 150 children with PWS and 46 children with AS linked to their survival status. Data on hospitalizations were available for 116 children with PWS and 42 children with AS from 8 registries (Table1).

Survival

A total of 7 children out of 150 with PWS died before the age of 10 years; a survival rate of 94.0% (95% CI 89.5-98.7%, Table 2). None of the deaths occurred during the first 4 weeks of life (Table 2). None of the 46 children with AS died within the first 10 years (Table 2).

Hospitalisation

Prader-Willi syndrome

During the first year of life, 86.2% (95% CI 69.9-94.0%) of children with PWS underwent hospitalization longer than 10 days (Table 3a). Additionally, nearly all infants (99.5%, 95% CI 97.6-99.9%) with this syndrome experienced at least one hospital stay during the first year after birth, with a median length of stay (LOS) of 25.3 days (95% CI 20.2-30.0 days, Table 3a). This proportion slightly decreased to 93.2% (95% CI 80.3-97.8%) for children aged 1-4 years, but LOS was significantly reduced to 1.2 days (95% CI 0.7-1.6 days) per year. A further decline was observed in older children aged 5-9 years, with 79.6% (95% CI 49.5-92.9%) of them being admitted to the hospital with a median LOS of 0.5 days per year (95% CI 0.3-0.8 days, Table 3a). Overall, the percentage of children with PWS requiring hospital admission was higher compared to children with any other major CA and the reference population, with differences widening particularly for older children (Figure 1a). Among infants aged less than 1 year, children with PWS had a hospital stay that was approximately three- and eight times longer compared to those experienced by children born with any other congenital anomaly and reference children, respectively (Figure 1b). However, these differences were not observed when comparing children aged 1-4 years (Figure 1b).

Angelman syndrome

Among children with AS, 59.0% (95% CI 39.6-74.0%) were admitted to the hospital in the first year after birth (Table 3b). Interestingly, this proportion is about 30% lower compared to those of infants born with any other CA who were hospitalized in the same life period (Figure 1a). A higher proportion of children with AS aged 1-4 years were hospitalized 95.3% (95% CI 81.8-98.9%), but this dropped to 68% (95% CI 40.0-85.0%) at 5-9 years (Table 3b).

The hospitalization rates for children with AS aged 1-4 and 5-9 years were higher than those of children with CA in the same age range (Figure 1a).

The median LOS for AS patients was 4.6 days (95% CI 2.6-6.5 days) in the first year of life, decreasing to 1.3 days per year (95% CI 0.6-2.0 days) in the 1-4-year age group, and to 0.6 days per year (95% CI 0.0-1.1 days) at 5-9 years (Table 3b and Figure 1b).

Surgery

Among children (0-4 years) with PWS syndrome, 61.4% (95% CI 42.9-75.5%) underwent a median of 2 surgical procedures (IQR 1-3), but only 6.9% (95% CI 1.5-18.5%) of them needed surgery during the first year of life (Table 4). Overall, the median age of first surgery was 81.9 weeks, IQR 52.7-144.6). Among children (0-4 years) diagnosed with AS, 31.4% (95% CI 15.5-48.6%) required a median of 2.5 surgical procedures (IQR 1-3), and 4% (95% CI 0.2-18.1%) underwent surgery in the first year (Table 4). Median age at first surgical procedure was 132.1 weeks (IQR 101.4-201.6) for children with AS.

DISCUSSION

In this study, we analysed a cohort of 150 children diagnosed with PWS and 46 children with AS, born in 1995-2014. These children were successfully linked to mortality and local healthcare databases in order to describe their health outcomes.

Prader-Willi syndrome

The heterogeneity in the genetic aetiology of PWS may explain differences in disease severity and reduced life expectancy [29]. A recent review of 110 key papers including data from 500 individuals with PWS, reported an average survival of 21 years, with obesity and obesity-related

complications as the primary cause of death [30]. Whittington et al. estimated a 3% annual mortality for individuals with PWS (0-47 years) [31] while other studies showed a survival probability of 80-87% (35-40 years) [32,33]. Overall, the most common causes of death among individuals with PWS are respiratory failure, cardiopulmonary factors, gastrointestinal complications and accidental deaths such as chocking [29,30,34]. However, it is difficult to gain a general understanding of PWS survival rate data due to differences in the selected study groups, age of individuals, and data collection methodologies. In this population-based study, encompassing a population of 5,681,558 births from 1995 to 2014, we found that children (0-9 years) diagnosed with PWS have a survival rate of 94% by 10 years of age, with no deaths occurring in the neonatal period.

Although the survival rate is high in the first 10 years of life, infants with PWS manifest severe muscle weakness and feeding issues leading to failure to thrive and lethargy, thus requiring frequent hospitalization during infancy [35]. A study conducted on 61 infants born in France in 2012 and 2013, showed that 93% of them were hospitalized in the neonatal period, and 84% of neonates required nasogastric tube feeding for an average duration of 38 days [36]. In our study, we found that almost all infants diagnosed with PWS needed hospitalization during the first year of life, with a median LOS of 25 days, and 86% of them had at least one hospital stay of 10 days or more (Table 3a).

Subsequently, while the majority of children required hospitalization, the average LOS was significantly reduced to 1.2 and 0.5 days per year, respectively, for the age groups 1-4 years and 5-9 years (Table 3a). Short duration of hospital admissions is unlikely to be associated with serious acute medical conditions [35]. Nonetheless, we observed that children with PWS typically underwent their first surgical procedure at approximately 1.5 years of age and had a median of 2

surgical procedures before 5 years of age. Surgical procedures at this age are primarily associated with the correction of cryptorchidism [37], adenotonsillectomy and orthognathic surgery to treat obstructive sleep apnea syndrome [38], all of which require short hospital stays.

In summary, although neonatal deaths are not observed, childhood mortality is high. The high rate of hospital admissions, the long hospital stays and the need for surgical interventions underscore the considerable impact of this syndrome on patients' lives.

Angelman syndrome

Most individuals with AS have a nearly normal life span, up to 60 or 70 years [39]. In line with these observations, we reported that no deaths occurred among children with AS by 10 years of age. Smith et al. observed that these infants may suffer from hypotonia at birth and feeding difficulties [40], consequently requiring hospitalization. Indeed, we observed that 59% of infants with AS needed hospital care in infancy with an average stay of 4.6 days (Table3). Hospitalizations become more frequent as children with AS grow older (95.3% at 1-4 years, 68% at 5-9 years) as they develop epilepsy and behavioural problems that might need management. We found that about 30% of children with AS undergo surgery before age 5 years (Table 4). In 2006 a long-term population-based study conducted by Thomson and colleagues reported that each person underwent a median of 5.5 hospital admissions (0-20 years) because of epilepsy, gastrointestinal disorders, and dental work among other reasons [9]. A few years ago, Khan et al. collected data from 302 individuals with AS (0-60 years): 68% of them had been hospitalized at least once since birth, with an average of 2.3 hospital admissions and a stay on average 4.5 days long [41]. The most common surgical procedures for children with AS included: insertion of ear tubes (34%), strabismus correction (30%), adenoidectomy and tonsillectomy (25), and gastrostomy tube

insertion/fundoplication [41]. Intervention can improve the overall quality of life of people with AS: they can achieve an appreciable level of integration, independence in tasks of daily life, and a good degree of ambulation and speech [42].

Strengths and limitations of the study

The key strength of this cohort study is its population-based approach, enabling the inclusion of all children diagnosed early in life with PWS and AS, rather than being restricted solely to cases reported to tertiary centres, as seen in previous studies. Furthermore, data on children diagnosed with PWS and AS were collected and validated by EUROCAT registries, which use standardized coding and definitions for all congenital anomalies, ensuring consistency across Europe, and a high level of case ascertainment. It is a strength of the study that the results include morbidity from birth to 10 years of age.

A potential limitation of this study is linkage failure which may also introduce a bias in the estimates of health outcomes. However, the overall linkage failure in EUROlinkCAT project was less than 5% and this usually occurred in the deaths occurring in the initial days of life before the newborns received a permanent name or identification number [21]. Since survival rates in the first days of life are high among children born both with PWS and AS, the bias introduced by linkage failure is likely to have a minor impact on health outcomes estimates from this study.

Some cases of PWS and AS with mild phenotype may have been diagnosed later in childhood or as young adults. In our study, most registries record children with congenital anomalies diagnosed within the first year of age, while some have no upper age limit. This may potentially under-estimate our results on children with Angelman syndrome which is often diagnosed later in life,

especially for milder phenotypes, but is unlikely to affect our results for Prader-Willi syndrome which is often diagnosed during the first year of life.

Conclusions

This study included children born with Prader-Willi syndrome and Angelman syndrome reported by European population-based Congenital Anomaly registries. The use of standardized and pooled data from 11 EUROCAT registries, provided robust analyses and accurate estimates of health outcomes for the children diagnosed prenatally or in early childhood. The results of the study are of primary importance for parental counselling and clinical management of patients with either of these two rare genetic diseases.

What is already known on this topic

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) significantly impact the lives of affected children. Most of the existing research typically address specific aspect of the disease, involves small case series or reports on broad age cohorts. Given the rarity of these two genetic syndromes, there is little population-based information on health outcomes of children with PWS and AS.

What this study adds

In this population-based cohort study, data from 11 EUROCAT registries, encompassing a population of 5,681,558 births, from 1995 to 2014, were analysed. We provided robust analyses and accurate estimates of survival rates, hospitalizations and number of surgical procedures of children born with PWS and AS.

How this study might affect research, practice or policy

Our findings are of primary importance for informing clinicians and counselling parents of children affected by these two rare genetic diseases. The results are especially valuable given the difficulty of obtaining population-level information about these two rare genetic syndromes.

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FIGURE LEGENDS

Figure1. Percentage of hospitalised (*a.*) and median length of stay per year (*b.*) for children with Prader-Willi syndrome, Angelman syndrome, children with any congenital anomaly and children without a congenital anomaly in 1995-2014.

a. Kaplan-Meier analyses were used to estimate the percentage of hospitalization for children with Prader-Willi syndrome ("PWS", light grey bar), Angelman syndrome ("AS", dark grey bar), children with any congenital anomaly ("All CA", black bar) and children born without a congenital anomaly ("Reference", white bar). Overall estimates were calculated for 3 age groups (<1 year, 1-4 years, 5-9 years) using a random effects meta-analysis. Error bars represent 95% confidence intervals.

b. The median length of hospital stay (LOS) per year was determined for children with Prader-Willi syndrome ("PWS", light grey bar), with Angelman syndrome ("AS", dark grey bar), children born with any congenital anomaly ("All CA", black bar) and children born without a congenital anomaly ("Reference", white bar). LOS was estimated by calculating the total number of days spent at hospital between the admission and discharge dates, for each registry. Random effects meta-analyses were performed for two age groups: < 1 year and 1-4 years. Error bars represent 95% confidence intervals.

TABLES

Table 1. Contributing European Surveillance of Congenital Anomalies (EUROCAT) registries with indication of included birth years and population covered.

Participating registries	Included birth years	Birth population covered[a]	Linkage to mortality data	Linkage to health care data
Finland[d]	1995-2014[b]	1,174,727	Yes	Yes
France: Paris	1995-2014	597,822	Yes	No
Italy: Emilia Romagna	2008-2014	282,094	Yes	Yes
Italy: Tuscany	2005-2014	299,869	Yes	Yes
Malta[d]	1995-2014	84,737	Yes	No
Norway[d]	1999-2014	956,939	Yes	No
Spain: Valencian Region	2007-2014[c]	403,099	Yes	Yes
UK: EM SY[e]	2003-2012	717,264	Yes	Yes
UK: Thames Valley	2005-2013	270,327	Yes	Yes
UK: Wales[d]	1998-2014	569,341	Yes	Yes
UK: Wessex	2004-2014	325,339	Yes	Yes
Total population		**5,681,558**		
Nb of children with Prader-Willi syndrome			**150**	**116**
Nb of children with Angelman Syndrome			**46**	**42**

[a] extracted from the EUROCAT website: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en, accessed on 30/09/2021; [b] study period for hospitalization 1997-2014; [c] study period for hospitalization 2010-2014; [d] whole country covered; [e] UK: East Midlands and South Yorkshire

Table 2. Pooled survival estimates adjusted for censoring at selected age groups up to 10 years of age for children born with PWS (n=150) between 1995 and 2014.

Prader-Willi Syndrome			
Age	**Number of deaths**	**% survival**	**95% CI**
1 week	0	100	97.6-100
4 weeks	0	100	97.6-100
1 year	3	96.9	94.2-99.7
5 years	5	96.2	93.2-99.3
10 years	7	94.0	89.5-98.7

Table 3. Percentage of hospitalization, percentage of hospitalization with a long stay (≥10 days) and median length of stay per year of children with *a.)* Prader-Willi syndrome and *b.)* Angelman syndrome in 1995-2014.

a.

	Prader-Willi Syndrome (n=116)							
	Children with any hospitalization			Children with a length of stay over 10 days*			Median length of stay	
Age	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**days**	**95% CI**
<1 year	115	99.5	97.6-99.9	79	86.2	69.9-94.0	25.3	20.2-30.4
1-4 years	97	93.2	80.3-97.8	6	n.c.		1.2	0.7-1.6
5-9 years	47	79.6	49.5-92.9	2	n.c.		0.5	0.3-0.8

b.

	Angelman Syndrome (n=42)							
	Children with any hospitalization			Children with a length of stay over 10 days*			Median length of stay	
Age	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**days**	**95% CI**
<1 year	26	59.0	39.6-74.0	2	n.c.		4.6	2.6-6.5
1-4 years	38	95.3	81.8-98.9	4	n.c.		1.3	0.6-2.0
5-9 years	19	68.0	40.0-85.0	1	n.c.		0.6	0.0-1.1

* Only children born ≥37 weeks of gestation included.

n.c. = not calculable: only registries with at least three cases were included in the meta-analysis

Table 4. Proportion of children with Prader-Willi syndrome (n=116) and Angelman syndrome (n=42) undergoing surgical procedures, in 1995-2014.

	Prader-Willi Syndrome			Angelman Syndrome		
Age	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
<1 year	11	6.9	1.5-18.5	2	4.0	0.2-18.1
1-4 years	64	60.5	44.0-73.5	13	31.6	15.6-48.9
0-4 years	67	61.4	42.9-75.5	13	31.4	15.5-48.6