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RESEARCH ARTICLE

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# The burden of disease for children born alive with Turner syndrome—A European cohort study

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## Abstract

**Background:** Turner syndrome is a rare congenital anomaly caused by complete or partial X chromosome monosomy that may affect mortality and morbidity in childhood.

**Methods:** This population-based data-linkage cohort study, as part of the EUROlinkCAT project, investigated mortality and morbidity for the first 5 years of life for liveborn European children diagnosed with Turner syndrome. Thirteen population-based registries in 10 countries from the European surveillance of congenital anomalies (EUROCAT) network participated. Data on children born 1995–2014 and diagnosed with Turner syndrome were linked to mortality,

hospital and prescription records. Children with any congenital anomaly and children without a congenital anomaly were included for comparison on morbidity.

**Results:** Out of a population of 5.8 million livebirths 404 were diagnosed with Turner syndrome prenatally or in infancy and 95.5% survived to their fifth birthday. During the first year of life 72.3% (95% CI 59.5;81.6) of children with Turner syndrome were hospitalized, the median length of stay was 5.6 days (95% CI 3.5;7.7) and 18.7% (95% CI 13.9;23.9) underwent surgery. After the first year of life hospitalizations and length of stay decreased but more children underwent surgery (30.8% [95% CI 17.6;44.7]). In the first 5 years the percentage of children with Turner syndrome having a prescription for antibiotics was 12%–20% per year and increased with the age of child.

**Conclusions:** In the first year of life, the burden of disease was relatively high for children with Turner syndrome. The outlook is more positive beyond the first year, though overall morbidity still exceeded that of children without congenital anomalies.

**KEYWORDS**

congenital anomaly, morbidity, survival, Turner syndrome

## 1 | INTRODUCTION

Turner syndrome is a sex chromosomal aneuploidy (45 X or 45 X mosaicism) in females, which may be diagnosed prenatally, after birth or later in life (Gravholt et al., 2019; Yesilkaya et al., 2015). It is primarily associated with physical symptoms, such as associated congenital anomalies, reduced height, lack of pubertal development and hence infertility (Gravholt, 2004; Gravholt et al., 2019; Yesilkaya et al., 2015).

The prevalence is estimated to be 5 per 10,000 live born females with a wide range from 2.5 to 21 per 10,000 females depending on method of testing and whether only children are included or also teenagers and adults and estimated number of affected spontaneously aborted fetuses (Gravholt, 2004; Hook & Warburton, 1983; Mortensen et al., 2012; Stochholm et al., 2006). Around half of the diagnosed cases are monosomy 45,X and the rest have mosaicism or other karyotypes (Gravholt et al., 2019; Yesilkaya et al., 2015). Studies have shown that 1 out of 10 are diagnosed prenatally with amniocentesis or chorion villus sampling after abnormal ultrasound findings such as hydrops fetalis or cystic hygroma or incidentally during the screening for other more severe chromosomal anomalies as Down syndrome (Gravholt et al., 2017; Swauger et al., 2021). The age of diagnosis ranges from 0 to 85 years for the different karyotypes as reported by Stochholm et al. (2006), but Swauger et al. (2021) reported a median age of diagnosis with a range from 4 to 18 years, and for those diagnosed after the first year of life the median age of diagnosis was 9.3 years.

Termination of pregnancy after prenatal diagnosis (TOPFA) may be offered to the pregnant woman and in some studies, termination was chosen in 70%–80% of the prenatally diagnosed cases (Christian et al., 2000; Stochholm et al., 2006). Data from the European Surveillance of Congenital Anomalies (EUROCAT, n.d.) have shown a prevalence of TOPFA for Turner syndrome at 1.59 (95% CI 1.52;1.67) per 10,000 births in 1995–2014 corresponding to 63% of the cases with Turner syndrome reported to EUROCAT with many of these also diagnosed with severe hydrops or a significant congenital heart defect (EUROCAT website 2022).

Turner syndrome is associated with increased mortality (Schoemaker et al., 2008) and increased morbidity (Gravholt et al., 1998; Yesilkaya et al., 2015) particularly due to associated cardiac and renal anomalies as well as endocrine disorders (Gravholt et al., 2017; Mortensen et al., 2012). Previous studies were often based on small sample sizes and were not including the general burden of disease compared to the background population. Studies describing survival and morbidity of young children diagnosed with Turner syndrome are limited. Information on mortality and morbidity in childhood is important for counseling of parents after a prenatal diagnosis of Turner syndrome.

This study was part of the EUROlinkCAT project, a European population-based record-linkage cohort study, that used the EUROCAT infrastructure to establish

**TABLE 1** Overview of the contributing EUROlinkCAT registries for which data were available for analyses for children with Turner syndrome.

| Registry | Birth years | Total births | Data on survival | Data on hospital stays | Data on surgeries | Data on antibiotic prescriptions |
|---|---|---|---|---|---|---|
| Denmark, Funen | 1995–2014 | 100,119 | Yes | Yes | Yes | Yes |
| Finland | 1995–2014 | 1,169,172 | Yes | Yes | Yes | Yes |
| France, Paris | 1995–2014 | 592,373 | Yes | No | No | No |
| Italy, Emilia Romagna | 2008–2014 | 281,309 | Yes | Yes | Yes | Yes |
| Italy, Tuscany | 2005–2014 | 299,089 | Yes | Yes | Yes | Yes |
| Malta | 2005–2014 | 40,737 | Yes | No | No | No |
| Netherlands, Northern | 2005–2010<br>2013–2014 | 139,269 | Yes | Yes | No | No |
| Norway | 1999–2014 | 948,013 | Yes | No | No | No |
| Spain, Valencian Region | 2007–2014 | 401,231 | Yes | Yes | Yes | Yes |
| UK, East Midland (EM) & Southern Yorkshire (SY) | 2003–2012 | 712,960 | Yes | Yes | Yes | No |
| UK, Thames Valley | 2005–2013 | 268,974 | Yes | Yes | Yes | No |
| UK, Wales | 1998–2014 | 566,470 | Yes | Yes | Yes | Yes |
| UK, Wessex | 2004–2014 | 299,644 | Yes | Yes | Yes | No |
| Total | | 5,819,360 | 13 registries | 10 registries | 9 registries | 6 registries |

standardized datasets containing information about survival and morbidity for children up to 10 years of age with major congenital anomalies (Morris et al., 2021). The aim of this study was to estimate the survival of liveborn children with Turner syndrome up to age 5 years and to examine morbidity measured as hospitalizations, length of stay in hospital, surgery and antibiotic prescriptions for children diagnosed prenatally or in infancy with Turner syndrome compared to all children with a congenital anomaly and to reference children.

## 2 | METHODS

This is a European, population-based data-linkage cohort study using routinely collected data from mortality databases and hospital discharge databases. The study includes data from 13 EUROCAT registries (national and regional) in 10 countries, see Table 1.

### 2.1 | Population

The inclusion criteria were all children born alive between 1995 and 2004 in the geographic areas covered by the EUROCAT registries and diagnosed with Turner syndrome prenatally or in infancy. The EUROCAT subgroup of Turner syndrome is based on the ICD9 code 7586 except 75,868 and the ICD10 code Q96. The registries include cases with confirmed karyotype anomalies only. The ICD9 and ICD10 codes for all liveborn children with Turner syndrome were checked in the EUROCAT central database for the same registries and birth years as included in this study, except for Finland. The data

extract showed that 35% had a code for karyotype 45X, 54% had a code for other Turner karyotypes including mosaicism and 11% had an unspecified code for Turner syndrome.

For registries included in the analyses of morbidity, we also included data on all children born with major congenital anomalies defined by EUROCAT as "All anomalies". All children without a congenital anomaly born in the same birth years and from the same geographical area covered by the registry were included as a reference population (reference children) (Morris et al., 2021). These two comparison groups included both girls and boys. The registry in Tuscany used a 10% random sample of their population as reference children and the Northern Netherlands registry used a random sample of 20% of their population for each birth year as reference children. For the three English registries information on reference children was not available.

All children in the study were followed from birth to their 10th birthday or to the end of 2015 whichever came first, thus all children had at least 1 year of follow-up.

## 2.2 | Data on survival

Data on survival were obtained for children diagnosed with Turner syndrome by linkage to vital statistics and death certificates and were available for 13 registries in 10 countries. The mortality rate for all liveborn children across Europe were obtained from the statistical office of the European Union (EU), EUROSTAT and converted to a survival rate for comparison of the survival for children diagnosed with Turner syndrome.

## 2.3 | Data on hospitalization

Data on hospitalizations and surgical procedures were obtained for all three groups of children by electronic linkage to the hospital databases used in the regions and countries. For the morbidity study, the linkage success was 97% for children with congenital anomalies and 95% for reference children. Further details of the linkage methods used in the EUROlinkCAT study have been published earlier (Morris et al., 2021; Urhoj et al., 2022). Data on hospitalization for children with Turner syndrome were available for 10 registries (Table 1). For 6 of the 10 registries the hospital databases covered hospital stays in the whole country. For Wales, hospital stays in England were included. For the Valencian Region in Spain and Emilia Romagna in Italy, the hospital databases covered the same region as the EUROCAT registry. Data on hospitalization for reference children and children with any congenital anomaly were obtained from the EUROlinkCAT study on hospitalizations (Urhoj et al., 2022). Data included length of hospital stays measured as the number of days in hospital per year and for term born children hospital stays of 10 days or more.

## 2.4 | Data on surgeries

Data on surgical procedures for all three groups of children were available for eight registries (Table 1). Surgical procedures were coded according to the coding systems used in the national health systems. Italy and Spain used ICD-9-CM (the International Classification of Diseases, 9th revision-Clinical Modification) for the study period, England and Wales used OPCS-4 (Classification of Interventions and Procedures) and Finland and Denmark used national adaptions of NCSP (NOMESCO Classification of Surgical Procedures). Three pediatricians from two European countries independently reviewed all the codes from the extensive lists of surgery and procedure codes from the six countries with the three different coding systems and reached consensus on which codes defined surgeries. The study variable "Any surgery" was included.

## 2.5 | Data on antibiotic prescriptions

Data on the number of antibiotics prescriptions were obtained by linking to electronic prescription databases in six registries. We included antibiotics codes beginning with J01 as defined by the WHO Anatomical Therapeutic Chemical (ATC) classification system. Data were included from the year 2000 or the first birth year included in the study by each registry up to the end of 2015. We estimated the proportion of children with Turner syndrome who received at least one antibiotic prescription up to age 5 years.

## 2.6 | Statistical analysis

A common data model was developed to standardize the variables from the hospital and prescription databases. This enabled all registries to run centrally written syntax scripts in Stata version 13 for linkage quality checks and analyses. The aggregated tables and analytic results produced were then sent to a Central Results Repository at Ulster University. No individual case data were shared.

All analyses were performed separately for two age groups: <1 year (0–364 days) and 1–4 years.

The number of days spent in hospital was calculated as using the day of admission and the day of discharge. If the date of admission and discharge occurred on the

same day, the length of stay was determined to be 0.5 days. Quantile estimation methods were used to obtain pooled estimates of the median number of days spent in hospital per year for those with at least one hospital admission in a random effects meta-analyses using the "metamedian" package in R, version 4.0.3.

In each registry, the percentages of children hospitalized and with surgeries within each age group were calculated using Kaplan Meier (KM) survival analyses to allow for the censoring on December 31, 2015, death or emigration. Pooled estimates of the percentage hospitalized and with surgery were calculated in random effects meta-analyses using the $\ln(-\ln(S(t)))$ transformation in STATA version 15. As only few children with Turner syndrome had extended hospital stays, the percentage with extended stays was calculated by summing the totals ignoring registry or censoring and the Wilson confidence interval for proportions was used.

## 3 | RESULTS

Between 1995 and 2014, 404 children were born and diagnosed with Turner syndrome prenatally or during infancy within the study areas. Total number of livebirths in the study areas was 5,819,360 giving a livebirth prevalence of Turner syndrome of 0.69 per 10,000 births (Table 1).

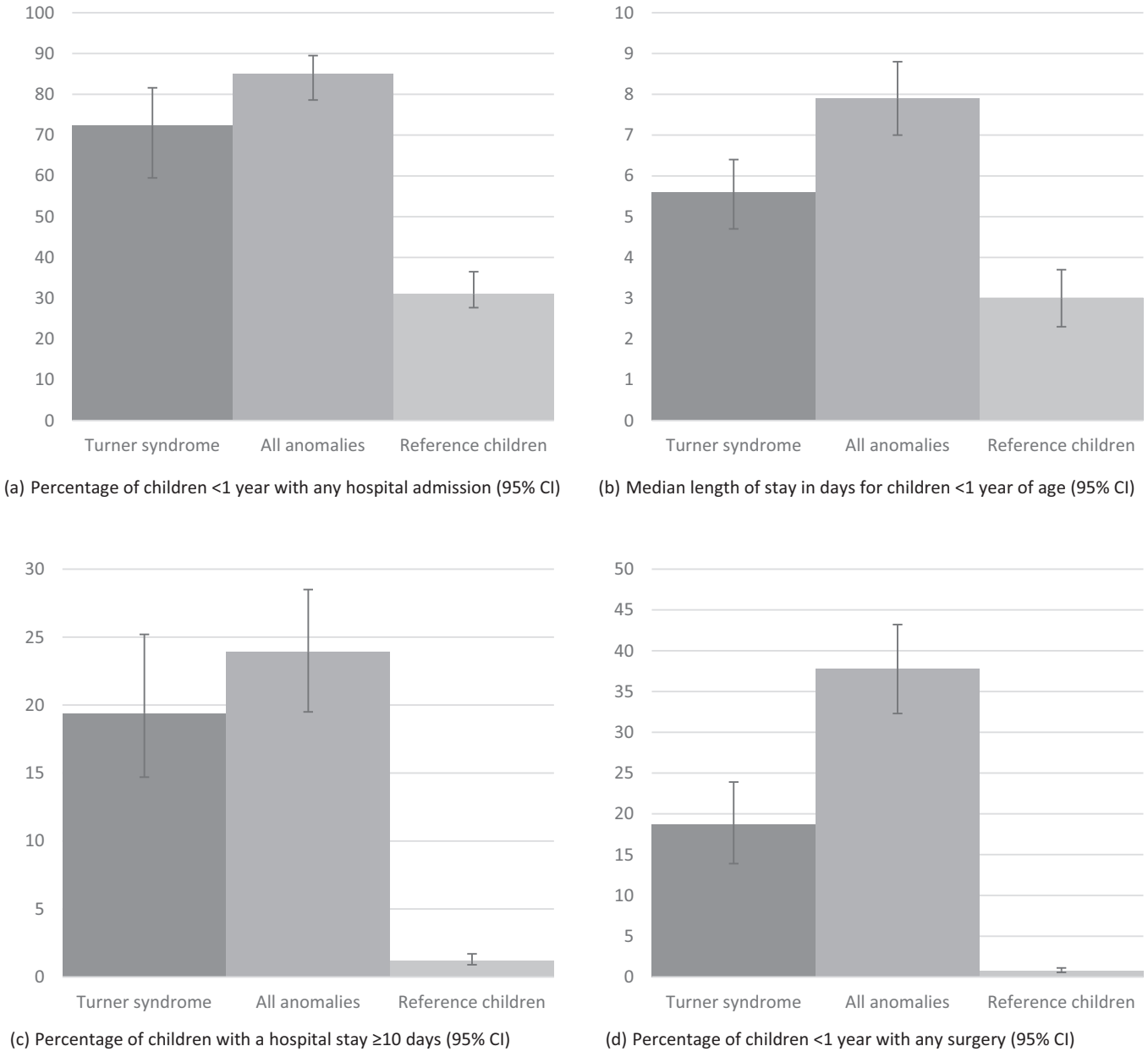
Eighteen of the 404 children diagnosed with Turner syndrome died within the first 5 years of life resulting in an overall survival rate of 95.5% at 5 years of age. There were less than three deaths after the first year of life.

For the morbidity analyses 300 children with Turner syndrome were included in the analyses of hospitalization and 260 children were included in the analyses of surgeries. During the first year after birth 72.3% (95% CI 59.5;81.6) of the children with Turner syndrome were admitted to hospital (Table 2). The proportion of children admitted to hospital at ages 1–4 years decreased as also occurred in the reference children. The median length of stay was 5.6 days (95% CI 3.5;7.7) in the first year and 19.4% (95% CI 14.7;25.2) of those born at term had a hospital stay of more than 10 days during the first year. For comparison with children with any congenital anomaly and reference children see Table 2 and Figure 1a–c.

During the first year 18.7% (95% CI 13.9;23.9) of children with Turner syndrome had surgery performed increasing to 30.8% (95% CI 17.6;44.7) of the children at

**TABLE 2** Data on hospitalization of children with Turner syndrome, children with any congenital anomaly and reference children in two age groups (<1 year and 1–4 years).

| Age group | Number of children | Number of children admitted to hospital | % of children with any hospital admission (95% CI) | Median length of stay in days (95% CI) | Number of children born at term | Number of children with a hospital stay ≥10 days | % of children with a hospital stay ≥10 days (95% CI) |
|---|---|---|---|---|---|---|---|
| <1 year | | | | | | | |
| Children with Turner syndrome | 300 | 213 | 72.3 (59.5;81.6) | 5.6 (3.5;7.7) | 216 | 42 | 19.4 (14.7;25.2) |
| Children with any congenital anomaly | 99,414 | 73,080 | 84.9 (78.6;89.5) | 7.9 (7.0;8.8) | 76,295 | 14,625 | 23.9 (19.5;28.5) |
| Reference children | 2,016,042 | 540,046 | 31.0 (25.7;36.5) | 3.0 (2.3;3.7) | 1,825,115 | 17,295 | 1.2 (0.9;1.7) |
| 1–4 years | | | | | | | |
| Children with Turner syndrome | 291 | 169 | 54.6 (39.0;67.8) | 0.5 (0.3;0.6) | 210 | 12 | 5.7 (3.3;9.7) |
| Children with any congenital anomaly | 94,555 | 50,829 | 56.2 (51.1;61.0) | 1.0 (0.7;1.2) | 73,793 | 3302 | 5.4 (4.8;6.1) |
| Reference children | 1,995,699 | 498,420 | 24.6 (18.8; 31.0) | 0.4 (0.2;0.5) | 1,803,378 | 7973 | 0.6 (0.5;0.8) |




(a) Percentage of children <1 year with any hospital admission (95% CI)

(b) Median length of stay in days for children <1 year of age (95% CI)

(c) Percentage of children with a hospital stay ≥10 days (95% CI)

(d) Percentage of children <1 year with any surgery (95% CI)

**FIGURE 1** Comparison of morbidity for children diagnosed with Turner syndrome, children with any congenital anomaly and reference children in the age group <1 year presented for (a) the percentage of children with any hospital admission (95% CI), (b) median length of stay in days (95% CI), (c) percentage of children with a hospital stay ≥10 days (95% CI), (d) percentage of children with any surgery (95% CI).

age 1–4 years. The median number of surgeries per child in the first year was 1.0 (95% CI 0.98;1.02) and the median age of first surgery was 4.9 weeks (95% CI 0.7;9) for surgeries performed in the first year of life (Table 3 and Figure 1d).

Prescription data were available from six registries for the period 2000–2015 and included 143 children with Turner syndrome. Figure 2 shows the percentage of these children who had a prescription for any antibiotics, by age of the child. The average percentage of antibiotic prescriptions increased with age. The proportion of children aged 4–5 years who had a prescription for antibiotics was 19.8%, compared to 11.5% for children aged <1 year.

## 4 | DISCUSSION

This study is the first population-based multi-center study to evaluate the burden of disease in terms of survival, hospitalization, surgery and prescriptions for antibiotic prescriptions for the first 5 years of life in children diagnosed with Turner syndrome prenatally or in

**TABLE 3** Data on surgeries for children with Turner syndrome, children with any congenital anomaly and reference children in two age groups (<1 year and 1–4 years).

| Age group | Number of children | Number children with any surgery | % of children with any surgery (95% CI) | Median number of surgeries per child (95% CI) | Median age of first surgery in weeks (95% CI) |
|---|---|---|---|---|---|
| <1 year | | | | | |
| Children with Turner syndrome | 260 | 47 | 18.7 (13.9;23.9) | 1.0 (0.98–1.02) | 4.9 (0.7;9) |
| Children with any congenital anomaly | 91,504 | 29,616 | 37.8 (32.3;43.22) | 1.78 (1.49;2.1) | 11.2 (9.5;12.9) |
| Reference children | 1,960,272 | 18,057 | 0.79 (0.55;1.11) | 1 (0.99;1.0) | 17.1 (11.9;24.3) |
| 1–4 years | | | | | |
| Children with Turner syndrome | 251 | 86 | 30.8 (17.6;44.7) | 1.6 (0.8;2.4) | 138.6 (103.1;173.9) |
| Children with any congenital anomaly | 87,129 | 26,427 | 34.5 (31.2;37.9) | 1.78 (1.49;1.07) | 94.4 (86.7;102.0) |
| Reference children | 1,935,199 | 141,465 | 6.25 (4.01;9.16) | 1 (0.99;1.00) | 167 (147.5;186.5) |

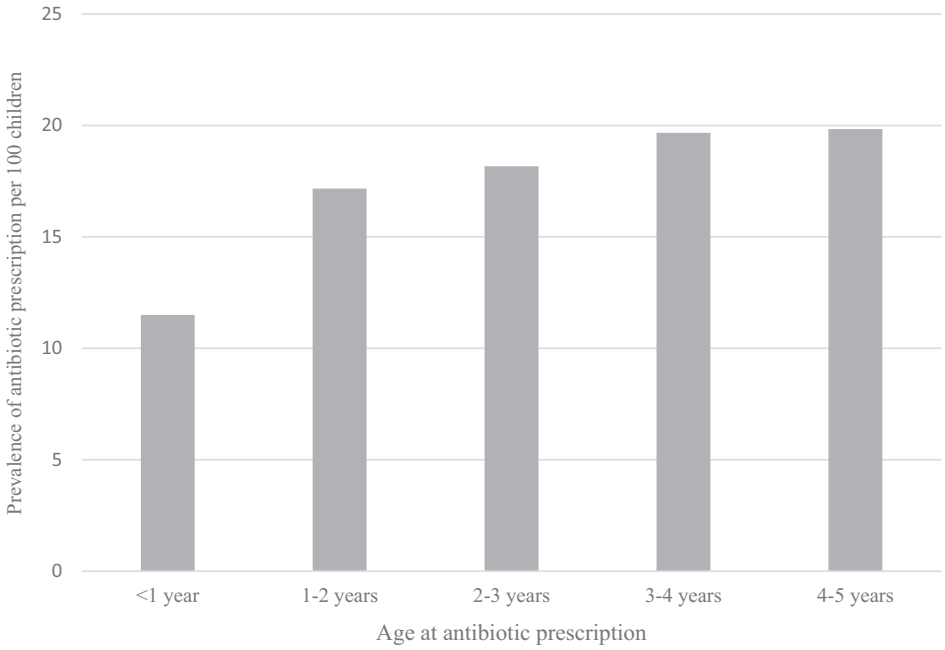



**FIGURE 2** Proportion of children with Turner syndrome who had an antibiotic prescription by age. Numbers are combined for all registries. Each child may appear in more than one age group.

infancy. The livebirth prevalence was 0.69 per 10,000 live births which is in line with the finding in other studies of 10% diagnosed prenatally and in infancy (Swauger et al., 2021). Our results can be applied to children diagnosed prenatally and shortly after birth with any of the karyotypes associated with Turner syndrome. Studies have described an association between the genetic expression, phenotypic expression, and the severity of comorbidities (Cameron-Pimblett et al., 2017; Tuke et al., 2019). In this study it was not possible to

distinguish the different karyotypes as they were analyzed as one group.

In 2009 the infant mortality rate among all live born infants across the EU was 4.2 deaths per 1000 live births (EUROSTAT website, 2021). This study showed a survival rate within the first 5 years of life for children with Turner syndrome at 95.5% with the majority of deaths in the first year, which gives a 10-fold higher mortality in infancy when compared to all liveborn children in EU. A British cohort study reported a three-fold higher overall mortality than the general population and the expected life span for adults diagnosed with Turner syndrome was reduced by 8–10 years (Schoemaker et al., 2008).

The overall morbidity for children with Turner syndrome was higher than for reference children and more comparable to children with any congenital anomaly. For both reference children and children diagnosed with Turner syndrome morbidity decreased after the first year of life. Our results are consistent with a higher burden of disease in early childhood for children with Turner syndrome. This is a result of associated comorbidities such as congenital heart defects and renal anomalies (Mortensen et al., 2012; Yesilkaya et al., 2015). Diagnosis such as coarctation of the aorta, bicuspid aortic valves and other aortic arch anomalies are estimated to affect 23%–50% of the children with Turner syndrome and will increase the proportion of hospitalization and the need for surgery (Gravholt et al., 2017; Mortensen et al., 2012; Urhoj et al., 2022). Children with Turner syndrome are more likely to be born moderate preterm and/or small for gestational age (Hagman et al., 2010) which also will increase the length of stay in hospital in the first year due to feeding problems. Another known issue for females diagnosed with Turner syndrome is short stature (Gravholt et al., 2019). During childhood growth hormone treatments are initiated to improve the final height. This requires continuing health care visits, but usually not hospitalizations and therefore most likely not contributing to the burden of disease in terms of hospitalization analyzed in this study (Bondy, 2007; Gravholt et al., 2017).

Our study showed that approximately 2 out of 10 children with Turner syndrome had surgery performed within the first year of life, increasing to 3 out of 10 at ages 1–4 years. We had no available data regarding the type of surgery, but surgical procedures are frequently required for the congenital heart defects, especially coarctation of the aorta and aortic arch anomalies associated with Turner syndrome. Alam et al. (2021) found an average age at the first surgery of 1 month for females <21 years with Turner syndrome and an associated congenital heart defect, which corresponds to the median age at first surgery of 4.9 weeks found in this study. Some of the surgical procedures in children with additional Y-chromosome material may be due to the recommended gonadectomy due to the risk of cancer, although this may be done after 5 years of age (Gravholt et al., 2017). Otological disorders may as well contribute to the percentage of children who undergo surgery as Lim et al. found that 18.9% of the girls with Turner syndrome had insertion of tympanostomy tubes and/or myringotomy performed at 0–5 years of age (Lim et al., 2020). Sometimes these procedures are performed as an outpatient visit, but due to the increased anesthetic risks that may be present for children with Turner syndrome and associated comorbidities, especially the cardiac anomalies, these surgeries are more likely to take place in hospitals (Liese et al., 2014).

We found that 20% of children with Turner syndrome aged 4–5 years received antibiotic prescription. These children frequently suffer from recurrent acute otitis media, tympanic membrane perforation and cholesteatoma (Bois et al., 2018; Lim et al., 2020). The study from UK found that within a period of 1 year 24% of children with Turner syndrome experienced recurrent otitis media at 0–5 years compared to <2% with three or more episodes of acute otitis media in the general pediatric population before 6 years of age (Lim et al., 2020). Children with Turner syndrome also has an increased risk of renal anomalies and therefore also increased risk of urinary tract infections (Yesilkaya et al., 2015).

Children with Turner syndrome diagnosed prenatally or in infancy may represent the most severe cases with early symptoms prenatally as lymphedema or webbed neck as well as those found incidental with prenatal testing (Swauger et al., 2021). The overall median age at diagnosis found by Schoemaker et al. was 14.5 years and it has been estimated that around 20% of the children diagnosed between 11 and 18 years due to short stature or lack of pubertal development may not show any symptoms earlier in childhood (Schoemaker et al., 2008; Swauger et al., 2021). It may be hard to distinguish these children from unaffected children and they will probably have a survival rate closer to the overall infant and childhood mortality rate as well as hospital admissions and surgeries more similar to the reference children in this study.

It is a limitation of the study that the two comparison groups included all children and not girls only as girls are less likely to be in hospital. A study from Australia found that boys were more likely to be admitted to hospital than girls for both the group of children with major congenital anomalies and for the children without congenital anomalies (Colver & Bower, 2009).

The decision to continue or terminate the pregnancy after a prenatally diagnosis of Turner syndrome may be

very difficult (Hermann et al., 2019; Jeon et al., 2012). Unbiased information about the prognosis and potential benefit of early diagnosis is important to discuss before taking a decision (Holm et al., 2021; Jaramillo et al., 2019; Wasserman & Asch, 2012). Results from this study will be useful in the counseling of parents after a prenatal diagnosis. Early diagnosis and knowledge about the risk of increased morbidity and lower first year survival is important for the physicians when counseling a couple expecting or having a child with Turner syndrome (Gravholt et al., 2017). This knowledge provides an opportunity to plan for a multispecialty team of health care providers to assist the family and plan the best possible care for the child and the family which enables early therapeutic intervention and managing comorbidities.

## 5 | CONCLUSION

The overall survival rate for live born children diagnosed early with Turner syndrome was 95.5% for the first 5 years of life. Children with Turner syndrome were more often hospitalized, they had longer stay and a higher proportion underwent surgery compared to children without congenital anomalies for the first 5 years of life. Antibiotic prescriptions increased with the age of child. The burden of disease for children diagnosed with Turner syndrome is rather high during the first year but improves later in childhood. Our results can be applied to the children diagnosed prenatally and shortly after birth.

### AUTHOR CONTRIBUTIONS

Joan Morris, Maria Loane and Ester Garne designed the EUROlinkCAT study and obtained funding. Ann-Louise Rud Andersen wrote the protocol for this study. Ann-Louise Rud Andersen, Stine Kjaer Urhoj and Joachim Tan analyzed the data. Amanda J. Neville, Anna Pierini, Babak Khoshnood, Clara Cavero-Carbonell, Diana Wellesley, Hermien E. K. de Walle, Kari Klungsoyr, Miriam Gatt, Mika Gissler and Ester Garne contributed with data from their EUROCAT registries. Maria Loane, Ieuan Scanlon and Stine Kjaer Urhoj performed the standardization of the variables. Joan Morris supervised the analysis scripts. Ann-Louise Rud Andersen wrote the first draft of the manuscript. All authors reviewed and revised the manuscript.

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### CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interests to disclose.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the participating registries of congenital anomalies, but restrictions apply to the availability of these data, which were used under license for the current study. These data are available for scientifically valid requests and with permission of the participating registries of congenital anomalies. To apply for the data please contact the corresponding author.

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