Hospitalizations in people with down syndrome across age groups: a population-based cohort study in Switzerland

Pascal Gaechter,[a,b,h,*] Fahim Ebrahimi,[c,d,h] Alexander Kutz,[e,f,g,i] and Gabor Szinnai[a,b,g,i]

[a]Pediatric Endocrinology and Diabetology, University Children's Hospital Basel UKBB, University of Basel, Basel, Switzerland
[b]Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland
[c]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[d]Department of Gastroenterology & Hepatology, University Digestive Health Care Center Basel – Clarunis, Basel, Switzerland
[e]Division of General Internal and Emergency Medicine, University Department of Medicine, Kantonsspital Aarau, Aarau, Switzerland
[f]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[g]Medical Faculty of the University of Basel, Basel, Switzerland

eClinicalMedicine
2025;80: 103062
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.103062

Summary

Background People with Down syndrome suffer from multiple associated diseases. However, knowledge on rates and causes of hospitalizations is limited.

Methods This population-based cohort study used national hospital claims data in Switzerland between January 1, 2012 and December 31, 2020. Included were hospitalizations of people aged 0–90 years. People with Down syndrome were identified using ICD-10-GM code Q90 and were compared to the general population. The primary outcome was the hospitalization rate. Secondary outcomes were the primary reasons for hospitalizations, secondary diagnoses, and in-hospital outcomes. Analyses were stratified by three age groups: neonates and infants (0–12 months), children and adolescents (1–17 years), and adults (18–90 years). We calculated incidence rates, risk ratios (RR), and regression coefficients with corresponding 95% confidence intervals (CI).

Findings Among 9,992,538 hospitalizations, 5697 were identified for people with Down syndrome. Hospitalization rate for people with Down syndrome was highest in the first two years of life. In the total general population, it was highest in adults beyond 60 years. Primary reasons for hospitalization among people with Down syndrome were classified as diagnoses of the circulatory system (neonates and infants: RR 13.3 [95% CI 12.0–14.6], children and adolescents: RR 3.3 [95% CI 2.7–3.9]), and infectious diseases (adults: RR 4.0 [95% CI 3.7–4.2]). At birth, individuals with Down syndrome typically had an average of six diagnoses, a number that the general population reaches, on average, by the age of 69. People with Down syndrome experienced worse in-hospital outcomes, including longer stays in both the hospital and intensive care unit by a factor of 1.7 and a higher all-cause in-hospital mortality by an overall rate difference of 1.9%.

Interpretation The findings underscore the medical complexity of hospitalized people with Down syndrome and emphasize the need for a comprehensive, age-inclusive approach to improve in-hospital outcomes and anticipate emergency hospitalizations across age groups.

Funding Kantonsspital Aarau AG.

Keywords: Down syndrome; Down's syndrome; Trisomy 21; Hospitalization rate; In-hospital outcome; Mortality

Introduction

Down syndrome, also known as Down's Syndrome or trisomy 21, was first described by John Langdon Down in 1866 as patients with intellectual disability, feeble circulation, delay in development, and common dysmorphia.[4] All karyotypes combined result in an

*Corresponding author. University Children's Hospital Basel UKBB, Spitalstrasse 33, Basel CH-4031, Switzerland.
E-mail addresses: Pascal.Gaechter@ukbb.ch, pgaechter@gmx.ch (P. Gaechter), fahim.ebrahimi@clarunis.ch (F. Ebrahimi), kutz.alexander@gmail.com (A. Kutz), Gabor.Szinnai@ukbb.ch (G. Szinnai).
[h]Shared first authors.
[i]Shared senior authors.

Research in context

Evidence before this study

We conducted a literature search in Pubmed for studies on diagnoses/co-morbidities among people with Down syndrome across the lifespan published up to December 31, 2023. The keywords used for the search were ("Down* syndrome" OR "trisomy 21") AND ("health*" OR "morbidit*" OR "co-moborbidit*" OR "diagnos*") AND ("lifespan*" OR "life span*" OR "age groups" OR "age-groups") AND ("general population" OR "population" OR "reference") which yielded 108 results. We also searched relevant articles cited by these reports.

There are numerous publications focused on specific health conditions in either adults or children with Down syndrome. However, only limited data exists to provide a comprehensive overview of hospitalization pattern of people with Down Syndrome across age groups. We identified a handful of studies analyzing historical data, data from family practices, and non-population-based studies.[1–3] To our knowledge, there is no recent, population-based study providing a comprehensive overview of hospitalizations of people with Down Syndrome compared to the general population.

Added value of this study

This study expands existing research by utilizing nationwide hospitalization records to investigate hospitalization rates, primary reasons for hospitalization, diagnoses, and in-hospital outcomes for people with Down syndrome compared to the general population. The findings offer a comprehensive view of the inpatient healthcare needs faced by this population.

Implications of all the available evidence

Since the life expectancy for people with Down syndrome has significantly increased in recent years, an increasing number of pediatricians, general practitioners, and medical specialists are treating individuals with Down syndrome. These healthcare providers need to be aware of the specific needs of this population, both in inpatient and outpatient settings. Along with recent evidence, our findings may facilitate the anticipation of emergency hospitalizations of people with Down syndrome across age groups and can help to update clinical guidelines.

incidence of Down syndrome of approximately 67–126 cases per 100,000 population years, with a male-to-female ratio of around 1–1.15.[5–8]

Clinically, Down syndrome is characterized by an increased risk of congenital malformations, dysmorphic features, and other health issues. At birth, the most important condition is congenital heart disease with a prevalence of about 50% of all people diagnosed with Down syndrome, compared with only about 0.5–1.2% in the general population.[9–14] Further important concomitant conditions include pulmonary arterial hypertension, congenital gastrointestinal anomalies, infections of the respiratory tract in childhood, leukemia, epilepsy, and Alzheimer disease.[15–24] A study from Japan found primary causes of mortality to be congenital heart disease and diseases of the circulatory system (predominantly in until the age of 50), pneumonia and respiratory infections, and aspiration pneumonia (both predominantly in advanced adulthood).[25] Life expectancy for Down syndrome has increased significantly in recent decades due to improved treatment, particularly for congenital heart disease, and was estimated to be around 58.6 years by a cohort study from Australia published in 2002.[26–29]

Many studies have been conducted to investigate concomitant conditions typically affecting people with Down syndrome. However, there are only very limited population-based studies analyzing the overall pattern and characteristics of hospitalized people with Down syndrome across age groups.[1–3] Notably, a historical population-based study in Denmark analyzed hospitalization rates and primary reasons for hospitalization of people with Down Syndrome from 1977 to 2008 across age groups and compared it to the general population. The same study found higher rate ratios for hospitalizations were found among people with Down syndrome, especially until the age of 20 years.[2] Furthermore, a recently published population-based study from the UK based on records from family practices (outpatient data only), assessed morbidities of people with Down syndrome across the lifespan and found, that compared to the general population, the population with Down syndrome showed significantly increased risk ratios for developing dementia, hypothyroidism, epilepsy, and hematological malignancies.[1] Hence, building on previous findings from non-population based, historical, and outpatient data, this study uses hospitalization records from 2012 to 2020 to examine hospitalization rates, primary reasons for hospitalizations, diagnoses and comorbidities, and in-hospital outcomes in people with Down syndrome compared to the general population. The findings of this study can enhance awareness and understanding of the overall complexity and specific morbidities in hospitalized people with Down syndrome, which may help to anticipate emergency hospitalizations.

Methods

Study design

This was a nationwide cohort study of all hospitalizations of people with Down syndrome and reference

people without Down syndrome in Switzerland between January 1, 2012 and December 31, 2020.

Hospitalization data were obtained from population-based administrative claims data provided by the Swiss Federal Office of Statistics (Bundesamt für Statistik, Neuchâtel, Switzerland). The database includes all Swiss inpatient discharge records from acute, general, and specialty care hospitals in Switzerland for both pediatric, and adult people. Hospitals in Switzerland are legally obliged to provide data on all hospitalizations. Hence, the dataset is a near 100% sample of all inpatient discharges in Switzerland. Individual-level data on patient demographics, healthcare utilization, hospital typology, medical diagnoses, diagnostic tests, clinical procedures, and in-hospital patient outcomes were provided for all hospitalized people in Switzerland. The data were de-identified due to a multiple-step anonymization process. Each hospitalization in this database was uniquely identified so that re-hospitalizations could be tracked. Medical diagnoses were coded using the International Classification of Disease version 10, German Modification (ICD-10 GM) codes (http://www.who.int/classifications/icd/en/). This study followed the Strengthening The Reporting of Observational studies in Epidemiology (STROBE) reporting guideline.[30]

Ethics

The Ethics committee Northwest and Central Switzerland (EKNZ) approved the study and granted a waiver of informed consent (Req-2021-01397).

Case ascertainment and patient population

Hospitalizations of people with Down syndrome were identified using ICD-10-GM code Q90. Eligible hospitalizations were of neonates/infants, children and adults up to 90 years of age, restricted by the following exclusion criteria: Birth as primary reason for hospitalization, length of stay >365 days, age > 90 years at time of hospitalization and hospitalizations at departments of psychiatry, ophthalmology, radiology, rehabilitation as well as in emergency practices and "other" departments. See Fig. 1 for patient flow chart. In Switzerland, hospitalizations are defined as in-clinic patient stays for >24 h. Hospitalizations of people with Down syndrome were compared with hospitalizations of people without the diagnosis of Down syndrome (defined throughout the manuscript as general population). Data on population size per age and year were obtained from the census data from the Swiss Federal Office of Statistics. Since the total, age-specific prevalence of Down syndrome is unknown, all hospitalization rates are calculated with the denominator of total population life years with no stratification for the diagnosis of Down syndrome (total population = general population + Down syndrome population). Hence, this paper compares trends in hospitalization rates between the patient groups and not absolute numbers.

Classification of primary causes of hospitalization and secondary diagnoses

We classified the primary causes of hospitalization and secondary diagnoses based on ICD-10 codes and classified these into six main disease groups as most relevant due to their prevalence and clinical importance: circulatory system (I00–I99), infectious diseases (A00–B99), digestive system (K00–K95), nervous system (G00–G99), neoplasms (C00–D49), and musculoskeletal system and connective tissue (M00–N99). Congenital malformations of the nervous system (Q00–Q07) were subclassified in the nervous system diseases, congenital malformations of the circulatory system (Q20–Q28) were subclassified in the circulatory system diseases, and congenital malformations of the digestive system (Q38–Q45) in the digestive system diseases, respectively. Furthermore, we classified the following infectious diseases classified elsewhere in ICD-10 as infectious diseases: respiratory infections (J00–J22), infectious arthropathies (M00–M02), inflammatory diseases of the central nervous system (G00–G09). Secondary diagnoses are defined diseases diagnosed according to ICD-10 and include both acute and chronic diagnoses. Physiognomic or expected features of Down syndrome could not be assessed, since they are not part of the ICD-10 catalogue and are hence not documented in the nationwide dataset used in this study.

Outcomes

The primary outcome was the number of hospitalizations characterized by the incidence rate of hospitalizations per 100,000 population person-years, displayed across age groups and stratified by primary reasons for hospitalization. Secondary outcomes comprised (i) the number of diagnoses per hospitalized patient over lifetime, (ii) length of hospital stay (LOS)—defined as days spent in the hospital during the hospitalization, (iii) intensive care unit (ICU) admission rate, (iv) mechanical ventilation rate, (v) length of ICU stay, (vi) all-cause in-hospital mortality, and (vii) 30-day all-cause hospital readmission.

Statistical analysis

Unless stated otherwise, categorical variables are expressed as number (percentage) and continuous variables as mean (standard deviation, SD). Normality was graphically assessed for continuous variables, and log transformation (natural logarithm) was applied to right-skewed distributions (hospital and ICU stay lengths) to improve normality. Parametric tests were deemed appropriate given the large sample size (central limit theorem). Hospitalization rates were calculated as incidence rates per 100,000 person-years (PY) in Switzerland for each year between 2012 and 2020 and across age groups. Analyses were stratified by three age groups: neonates and infants (0–12 months), children and adolescents (1–17 years), and adults (18–90 years).

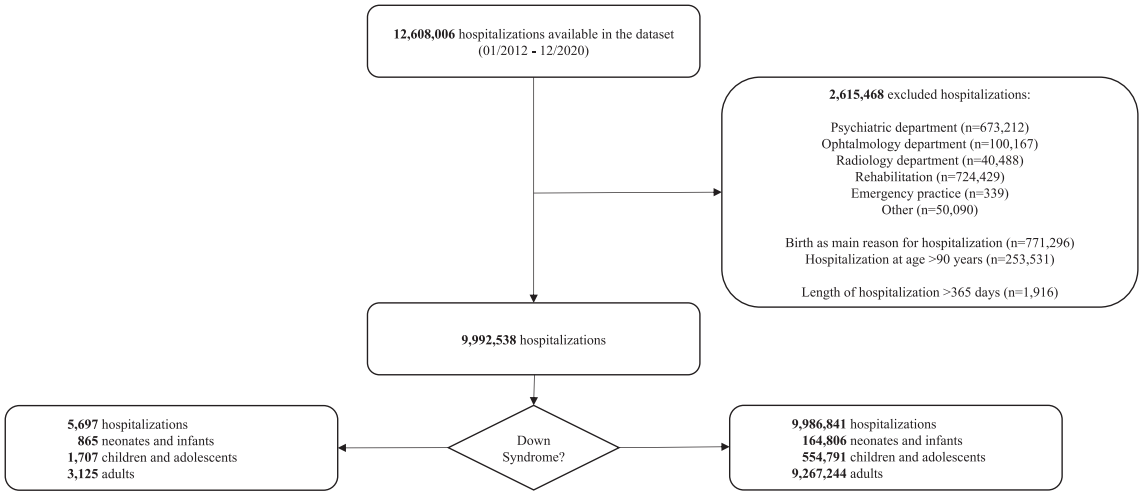

Fig. 1: **Hospitalizations flow chart.** Flow chart to illustrate included and excluded cases stratified by the diagnosis of Down syndrome and age groups.

The categorization of these three, straight-forward age groups was decided before analysis of the data and based on clinical judgement, since these are the most distinct age-groups. All risk ratios were calculated relative to an age-matched control group in the general population by direct computation based on observed frequencies (with riskratio.wald function in RR Studio). Due to the nature of our dataset, risk ratios are conditional on hospitalization (interpretation example for primary reason of hospitalization: given hospitalization, what is the likelihood of it being related to the circulatory system.) The confidence intervals were calculated using normal approximation (95% confidence interval). Since the risk ratios are conditional on hospitalization, they are unaffected by the differing age distribution in people with Down syndrome compared to the general population (due to a lower life expectancy). The calculation of this estimate was performed in age-matched reference people by 10 age groups: neonates and infants (0–12 months), 1–9 years and every decade thereafter until the age of 89 years. This age-categorization was equally decided before analysis of the data and based on clinical judgement. Local polynomial regression fitting was calculated using the loess function (with stats package in R Studio). To compare rate differences between people with Down syndrome to the general population, regression coefficients were used with a 95% confidence interval. The regression coefficients were derived from univariate models. Due to right-skewed distribution of length of hospital stay and length of ICU stay, we transformed these variables using logarithmic scale (natural logarithm). We performed a sensitivity analysis using multivariate models to test the robustness of our findings by additional adjustment for the covariates age and sex, hospital type, department type, patient complexity (measured by number of diagnoses), and the diagnosis of congenital heart disease. Since these covariates are influenced by Down syndrome, they are not purely confounders but also key explaining factors for the differences between the groups. All statistical analyses were performed using R Studio, version 1.3.1093. A two-sided $p < 0.05$ was considered statistically significant.

Role of funding source

No funding source had any role in any part of the study design, writing of the manuscript or any aspect pertinent to the study.

Results

Patient characteristics

From January 1, 2012, to December 31, 2020, we identified 5697 hospitalizations of people with Down syndrome (865 neonates and children, 1707 children and adolescents, 3125 adults) and 9,986,841 hospitalizations of reference people from the general population (164,806 neonates and children, 554,791 children and adolescents, 9,267,244 adults). The study flowchart of hospitalizations is depicted in Fig. 1. The mean age of all hospitalized people in Switzerland with Down syndrome was 28.2 ± 24.0 years compared to 54.5 ± 23.1 years in the general population. While the majority of hospitalized people with Down syndrome were male (61.3%), the proportion was 46.5% in the general population (Table 1). In total, 2572/5697 (45%) of hospitalizations of people with Down syndrome occurred in pediatric age (i.e., before the age of 18 years) while in the general population only 719,597/9,986,841 (7%) of all hospitalizations were pediatric cases.

	Neonates & infants		Children & adolescents		Adults		Total	
	Age 0–12 months		Age 1–17 years		Age 18–90 Years		Age 0–90 years	
	Down syndrome	General population	Down syndrome	General population	Down syndrome	General population	Down syndrome	General population
Number of hospitalizations	865	164,806	1707	554,791	3125	9,267,244	5697	9,986,841
Length of hospital stay (days)								
Mean (SD)	8.3 (3.2)	2.9 (2.7)	3.4 (2.7)	2.1 (2.2)	4.5 (2.6)	3.7 (2.5)	4.5 (2.8)	3.6 (2.5)
Regr. coeff. (95% CI)	2.9 (2.6–3.1)	Reference	1.6 (1.6–1.7)	Reference	1.2 (1.2–1.2)	Reference	1.7 (1.7–1.8)	Reference
ICU admission								
n (%)	396 (45.8)	21,447 (13.1)	380 (22.3)	24,078 (4.3)	428 (13.7)	647,518 (7.0)	1204 (21.1)	693,043 (6.9)
Rate diff. in % (95% CI)	32.8 (30.5–35.0)	Reference	18.0 (17.0–18.9)	Reference	6.7 (5.8–7.6)	Reference	14.2 (13.6–14.9)	Reference
Mechanical ventilation								
n (%)	283 (32.7)	12,165 (7.4)	139 (8.1)	8325 (1.5)	214 (6.8)	215,587 (2.3)	636 (11.2)	236,077 (2.4)
Rate diff. in % (95% CI)	25.3 (23.6–27.1)	Reference	6.6 (6.1–7.2)	Reference	4.5 (4.0–5.1)	Reference	8.8 (8.4–9.2)	Reference
Length of ICU stay (hours)								
Mean (SD)	101.9 (3.5)	73.1 (3.8)	39.0 (3.4)	34.4 (3.2)	55.8 (3.3)	34.7 (3.1)	60.7 (3.6)	35.5 (3.1)
Regr. coeff. (95% CI)	1.4 (1.2–1.6)	Reference	1.1 (1.0–1.3)*	Reference	1.6 (1.4–1.8)	Reference	1.7 (1.6–1.8)	Reference
In-hospital mortality								
n (%)	16 (1.8)	782 (0.5)	17 (1.0)	718 (0.1)	187 (6.0)	192,413 (2.1)	220 (3.9)	193,913 (1.9)
Rate diff in % (95% CI)	1.4 (0.9–1.8)	Reference	0.9 (0.7–1.0)	Reference	3.9 (3.4–4.4)	Reference	1.9 (1.6–2.3)	Reference
30-day readmission								
n (%)	141 (16.3)	11,143 (6.8)	243 (14.2)	30,596 (5.5)	326 (10.4)	707,004 (7.6)	710 (12.5)	748,743 (7.5)
Rate diff in % (95% CI)	9.5 (7.9–11.2)	Reference	8.7 (7.6–9.8)	Reference	2.8 (1.9–3.7)	Reference	5.0 (4.3–5.6)	Reference

SD, standard deviation; CI, confidence interval; n, absolute number; Regr. Coeff., Regression coefficient; Rate diff., Rate difference; ICU, intensive care unit. All 95% confidence intervals in Table 1 show statistical significance at the 95% confidence level since they do not cross 1.0 for regression coefficients and do not cross 0.0 for rate differences in %. All p-values in Table 1 are <0.0001, except for the p-value of length of ICU stay in the age group 1–17 years with a p-value of 0.037 (*). Regression coefficients shown in this table are derived from univariate models.

Table 1: **In-hospital outcomes stratified by age groups in people with down syndrome and the general population.**

Hospitalizations of any cause

People with Down syndrome had a proportion of hospitalizations as neonates and infants, and as children and adolescents than the general population, in which most hospitalizations occur during adulthood and especially the last decades of life. For people with Down syndrome, the highest incidence of hospitalizations was observed during the first year of life with 0.11/100,000 PY (Fig. 2). Due to shorter life-expectancy compared to the general population, the hospitalization rate of people with Down syndrome strongly decreased beyond 55 years of age. While there were no hospitalizations of people with Down syndrome beyond the age of 81 years, the hospitalization rates continuously increased in the general population up to the age of 90 years (Fig. 2). Hospitalization rates stratified by sex showed higher hospitalization rates for males with Down syndrome than females with Down syndrome at all ages. In the general population there is an important peak of hospitalizations among hospitalizations of females only due to births in early adulthood, which is non-existent in the Down syndrome population (Supplementary Fig. A1).

Causes of hospitalization

The primary causes of hospitalization strongly differed between people with Down syndrome and those from the general population for all explored age groups (Table 1).

In the first year of life, diseases of the circulatory system (risk ratio (RR) 13.3 [95% CI 12.0, 14.6]) and the nervous system (RR 3.28 [95% CI 2.41, 4.47) were more common causes of hospitalization in people with Down syndrome compared with age-matched reference people from the general population. In contrast, people with Down syndrome were at lower risk for hospitalization due to infectious diseases (RR 0.75 [95% CI 0.67, 0.84]). In childhood and adolescence, risk ratio for four of six primary hospitalization reasons were significantly higher in people with Down syndrome compared to hospitalized children and adolescents without Down syndrome: circulatory system risk ratio 3.25 [95% CI 2.74, 3.85], neoplasms risk ratio 2.2 [95% CI 1.9, 1.26], nervous system risk ratio 2.09 [95% CI 1.74, 2.51], and infectious and parasitic disease risk ratio 1.62 [95% CI 1.49, 1.75]. In adults, risk ratios were higher for two main disease groups for people with Down syndrome (infectious and parasitic disease risk ratio 3.97 [95% CI 3.71, 4.24], nervous system risk ratio 3.4 [95% CI 3.02, 3.82]). In contrast, risk ratio for hospitalizations for three main disease groups was significantly lower in people with Down syndrome compared to the general

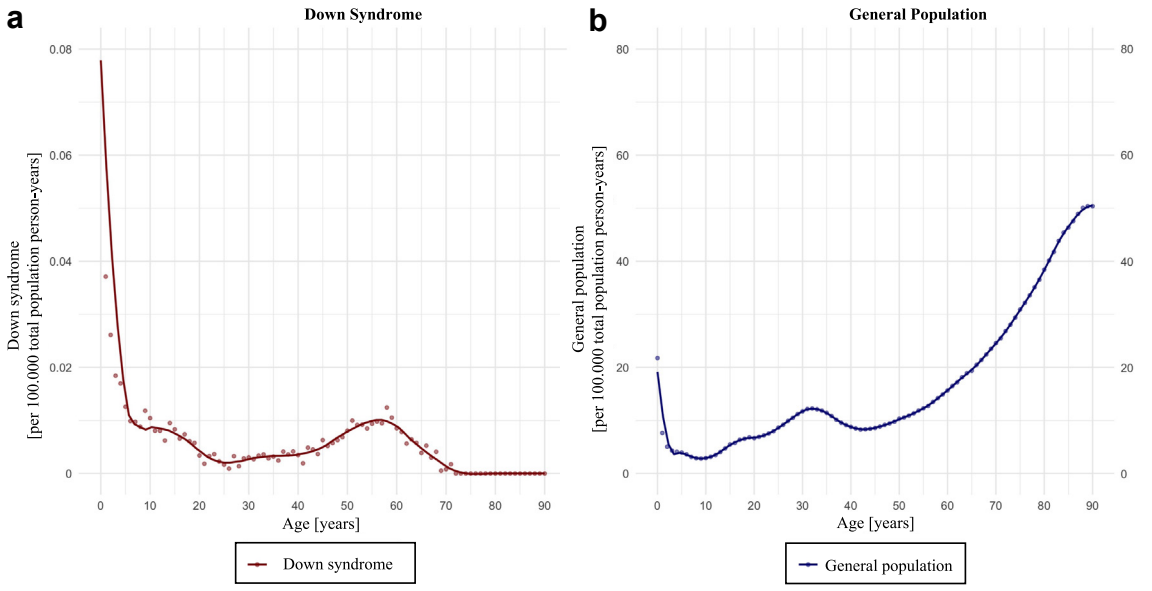

***Fig. 2:* Hospitalization rate of any cause.** Shown are hospitalization rates per 100,000 total population person-years for people with Down syndrome in 2a, and the general population without Down syndrome in 2b. Absolute numbers are not comparable (differing y-axis). Lower life expectancy in people with Down syndrome results in smaller peaks at older ages.

population: neoplasms risk ratio 0.41 [95% CI 0.34, 0.48], musculoskeletal system risk ratio 0.41 [95% CI 0.36, 0.47], and circulatory system risk ratio 0.74 [95% CI 0.66, 0.83].

Age-dependent conditional risk ratios (given hospitalization) between people with Down syndrome and people from the general population were calculated to compare the relative risk of i) a hospitalization being due to a specific disease group and ii) the presence of a specific secondary diagnosis in Fig. 3. In Fig. 4 the hospitalization rate across the lifespan is shown by disease category as continuous lines.

Number of diagnoses per hospitalization

People with Down syndrome already had an average of six diagnoses at the age of neonates and infants, with only a small increase during adulthood to an average of around seven diagnoses per patient (Fig. 5). In contrast, hospitalized people from the general population had approximately three diagnoses at birth, with a strong increase after the age of 45. At the age of 69 years, the general population had as many diagnoses as people with Down syndrome at birth and the number of diagnoses was equal between groups at the age of 76 years (Fig. 5).

Until adulthood people with Down syndrome had significantly higher risk ratios for 10 out of 14 selected diagnoses ranging from 3.1–46.3 in the first year of life, and 3.0–22.0 from 1 to 17 years (see details in Fig. 3 and Supplementary Table A1). In adults (18–89 years) risk ratios were lower for seven out of 14 selected diagnoses ranging from 0.1 to 0.8 and significantly higher for six out of 14 diagnoses ranging from 2.1 to 158.4.

In-hospital outcomes

People with Down syndrome had on average a significantly longer length-of-hospital stay compared with people from the general population, with a between-group factor of 2.9 in the first year of life and 1.6 during childhood and adolescence, and 1.2 in adulthood (Table 1). Correspondingly, ICU admission rates as well as mechanical ventilation rates were higher in all age groups of people with Down syndrome, most notably during the first year of life with an ICU rate difference of 25% and during childhood and adolescence with an ICU rate difference of 18%. Likewise, the 30-day readmission rate was significantly higher in all age groups for people with Down syndrome. Moreover, all-cause in-hospital mortality was significantly higher for people with Down syndrome in all age groups independent from hospitalization cause with 3.9% for people with Down syndrome versus 1.9% for the general population (Table 1). Neonates and infants with Down syndrome deceased in 1.8% of hospitalizations (rate difference of 1.4% [95% CI 0.9–1.8]), children and adolescents in 1.0% (rate difference of 0.9 [95% CI 0.7–1.0]), and adults in 6.0% (rate difference of 3.9 [95% CI 3.4–4.4]).

To check for possible confounding, we adjusted all regression models for age, sex, hospital type and department type. The figure is displayed in the appendix (Supplementary Fig. A2). While adjusting for sex and age alone minimally changes most estimates, combined

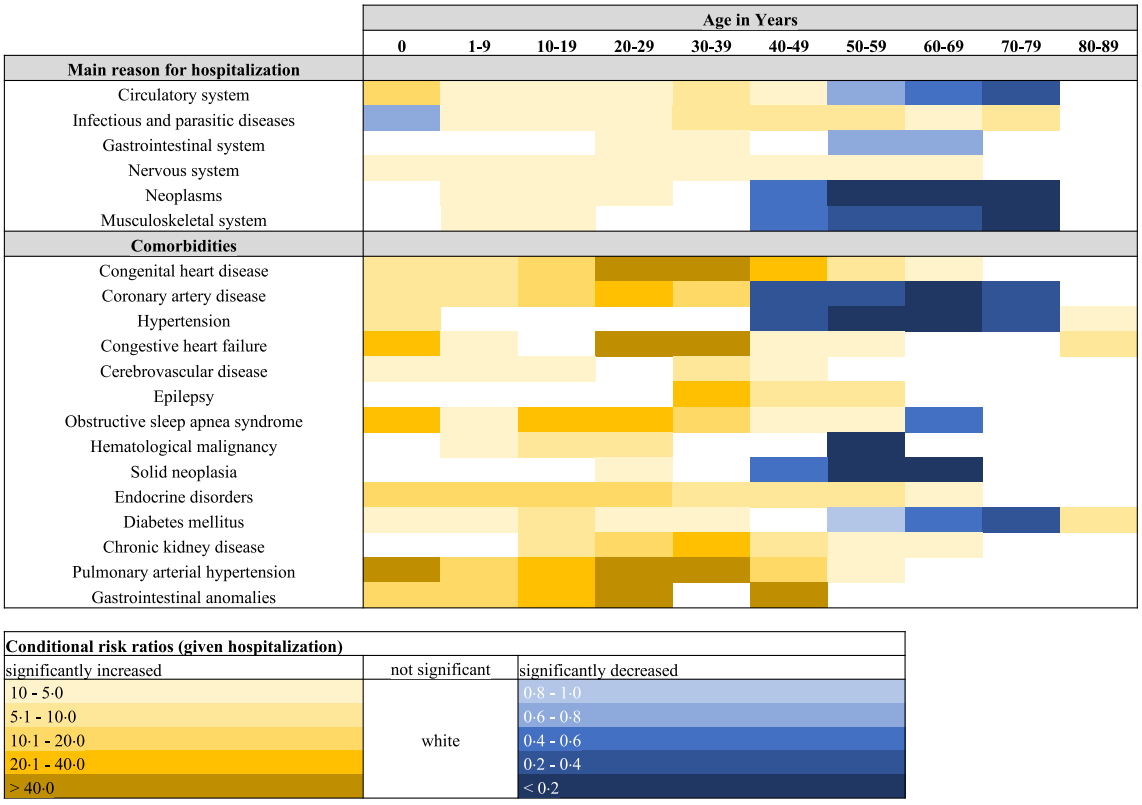

***Fig. 3*: Conditional risk ratios for primary reasons for hospitalization and diagnoses in individuals with Down syndrome compared to the general population.** The analysis examines conditional risk ratios (given hospitalization) for primary reasons for hospitalization and associated diagnoses. The interpretation addresses the likelihood that a hospitalization is attributed to specific causes, such as circulatory system diagnoses, within the context of the total number of hospitalizations. Notably, the total number of hospitalizations among individuals with Down syndrome above the age of 70 is small, as highlighted in Fig. 2, which should be considered when interpreting the findings. In the visual representation: Shades of yellow indicate that individuals with Down syndrome are hospitalized or diagnosed more frequently for a given condition. Shades of blue indicate that the general population is hospitalized or diagnosed more frequently. Ratios that are not statistically significant (95% confidence interval includes 1.0) are left unshaded (white).

adjustment with hospital type and department type marginally diminishes most estimates. Adjusting for the factors mentioned previously, as well as patient complexity (measured by the number of diagnoses) or the diagnosis of congenital heart disease, reduced most of the estimates. Notably, additional adjustments for patient complexity and congenital heart disease eliminated the differences in mortality observed in the 0–12 months age group.

Discussion

This population-based cohort study is based on all medical hospital admissions in Switzerland between January 1, 2012 and December 31, 2020 and is investigating the health-care burden of occurring conditions associated with Down syndrome across age groups. There are three key findings: First, people with Down syndrome had an at least five-fold higher hospitalization rate during early life until adolescence when compared to the general population. Second, the mean number of diagnoses of a patient at birth with Down syndrome is the same as that of a patient without Down syndrome at the age of 69. Third, when hospitalized, people with Down syndrome have significantly worse in-hospital outcomes compared to the general population with significantly longer length of hospital and ICU stays and higher in-hospital mortality rates.

To date, there is limited data on the incidence of hospitalization in people with Down syndrome compared with the general population across age groups. Our study showed that pediatric people with Down syndrome had a higher rate of hospitalization compared to the general population. This is in line with the existing data on this subject from nationwide studies in Denmark, France, Scotland, and European data.[2,3,31,32] In all studies, the hospitalization rate was highest in the first years of life. Two epidemiologic observations may

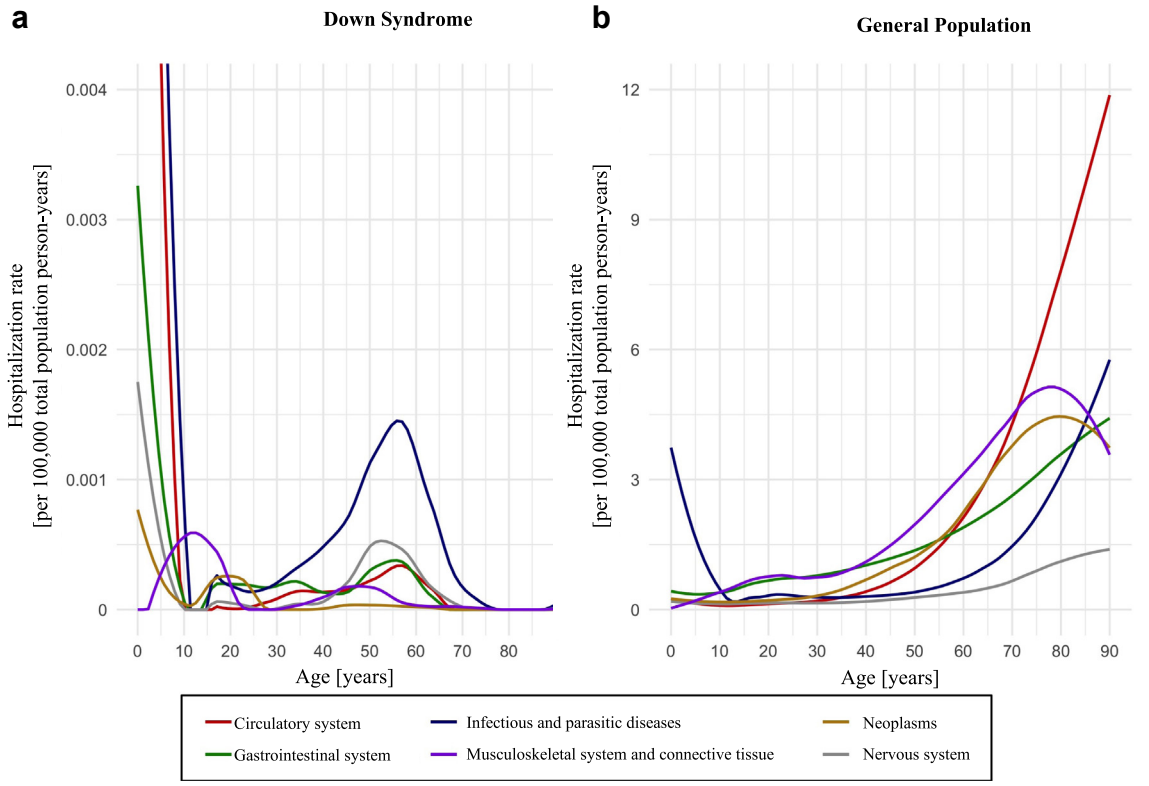

Fig. 4: **Hospitalization rates by disease categories.** Depicts the hospitalization rate of the six most important disease categories across the lifespan from 0 to 90 years of life. The hospitalization trends can be compared between people with Down syndrome (Figure 4a) versus the general population (Figure 4b). Absolute numbers are not comparable (differing y-axis). The disease categories depicted are: circulatory system (red), infectious and parasitic diseases (blue), neoplasms (brown), gastrointestinal system (green), musculoskeletal system and connective tissue (purple), and nervous system (grey).

contribute to this result: First, overall prevalence at birth of congenital heart disease in people with Down syndrome was previously found to be around 50% compared to only about 0.5–1.2% in the general population, and people with congenital heart disease are likely to be hospitalized more often than people without heart disease.[7,9–14] Second, survival of children born with Down syndrome with or without congenital heart disease is as high as 96% at ten years of age according to a meta-analysis from 2002, explaining a high hospitalization rate in the pediatric age group.[33] Compared to the pediatric age period, hospitalization rates were lower in young adulthood for people with Down Syndrome. This has been described before in a French study, which analyzed hospitalization rate of people with Down syndrome in four categories (short hospitalization stay, short hospitalization stay admission by emergency department, rehabilitation and psychiatric hospitalizations) and observed the lowest hospitalization rate for short hospitalizations and short hospitalizations by emergency hospitalization between 20 and 50 years of age.[3] In addition, our study showed a lower rate of hospitalizations per total population in adult people with Down syndrome compared to the general population, which may at least in part be caused by the differing life expectancy. In fact, life expectancy for people with Down syndrome was found to be 58.6 years in Australia in

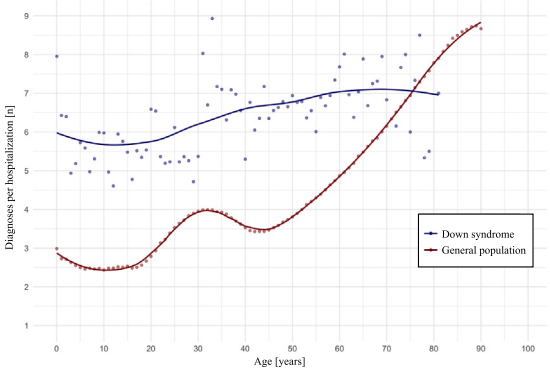

Fig. 5: **Number of diagnoses per hospitalized patient across the lifespan.** The number of diagnoses per hospitalization are depicted across all ages from 0 to 90 years.

2002, compared to a life expectancy of the general population of 82.8 years in Switzerland.[34,35] These results are consistent with our data, showing a decreased number of hospitalizations beyond the age of 55 years and no hospitalizations after age 81 among people with Down syndrome. Consistent with our findings, the only two studies to date also providing data on adult hospitalization rates, showed comparable hospitalization rates to this study in adult people with Down syndrome compared to the general population.[2,3] However, overall life expectancy in Down syndrome has increased substantially in recent decades and may continue to do so due to the improved treatment, particularly for congenital heart disease.[26–29,36,37] We may therefore expect to see a higher proportion of people with Down syndrome in adult hospitals in the future.

Our data show that people with Down syndrome had disease-specific and age-specific primary reasons for hospitalization, which were clearly different from the general population in each age group. This finding is well-aligned with a recently published study on diseases in people with Down Syndrome across the lifespan based on outpatient data, which showed significantly increased risk ratios for developing dementia, hypothyroidism, epilepsy, and hematological malignancies.[1] Based on our inpatient dataset, we found problems of the circulatory system, the nervous system and neoplasms were primary reasons for hospitalizations with significantly higher conditional risk ratios in people with Down syndrome than in the general population from birth to adulthood in accordance with earlier reports.[2,3] An explanation is offered by previous studies, which have shown that not only congenital heart disease is a common concomitant condition to Down syndrome, but also pulmonary arterial hypertension, which is usually diagnosed in the first year of life, and epilepsy as well as Alzheimer disease, more frequently diagnosed in adulthood,[15,18–21] In contrast, adults with Down syndrome were significantly less likely to be hospitalized for conditions of the circulatory system, neoplasm and musculoskeletal system than the general population. On the one hand, this may be due to the shorter life expectancy of people with Down syndrome.[34] On the other hand, the relatively lower importance of neoplasms correlates well with previous research which has found people with Down syndrome to be at a lower risk of solid cancer compared to the general population, albeit a 10–20 fold increased lifetime risk for leukemia compared to the general population.[23,24] During the first 10 years of life, infectious and parasitic diseases were a major reason for hospitalizations in both people with and without Down syndrome. In fact, for children with Down syndrome, previous studies from Israel and Australia have identified infections of the respiratory tract to be one of the most significant health issues.[22,38] In adults with Down syndrome, there was a second peak between the age of 40 and 65, with no corresponding rise among controls. This is in line with previous finding that respiratory infections are the primary reasons for death in people with Down syndrome.[25,31,39] Although endocrine disorders are rarely the primary reason for hospitalization, it is worth noting that the frequency of endocrine diseases in hospitalized people with Down syndrome was much higher compared with people without Down syndrome in all age groups. This finding may be related to previous findings that endocrine disorders are associated with Down syndrome, especially congenital hypothyroidism.[1,3,40] Diabetes mellitus occurring during childhood was more frequent in people with Down syndrome, while it occurred more often in the general population during adulthood. Consistent with this, previous studies have found that type 1 diabetes mellitus is more common in people with Down syndrome.[40,41] It is also interesting to note, there was a peak in hospitalization rates in the general population between the age of 25–40, with no corresponding peak of hospitalization rates in people with Down syndrome. This peak is likely to be due to pregnancy-related hospitalizations, as it was predominantly seen in hospitalizations of females (Appendix, Supplementary Fig. A1). Although it is known that women with Down syndrome are generally fertile, women with Down syndrome less frequently become pregnant.[42–44]

Neonates with Down syndrome had an average of six diagnoses, increasing to seven over the course of their lives, a number not reached until the age of 69 in the general population. This greater medical complexity at birth is likely to contribute further to the observed higher hospitalization rate of people with Down syndrome in the pediatric age group as outlined above. Finally, our data showed poorer in-hospital outcomes for people with Down syndrome compared to the general population in all age groups for all aspects measured. The longer length-of-hospital stay, particularly in the first year of life, has previously been described in similar extent as in our data set in Scotland for the first year of life, and in a European cohort for the first four years of life.[32,45] However, our data add to current knowledge six dimensions of in-hospital outcome (length of hospitalization, ICU-admission, mechanical ventilation, length of ICU stay, 30-day readmission, in-hospital mortality), and, for the first time, provides data across age groups. To our knowledge, there is no earlier research to support or contradict our findings of a dramatically increased ICU admission rate, longer duration of mechanical ventilation or a longer mean length of stay at the ICU in people with Down syndrome. We observed a higher in-hospital mortality for all age groups with Down syndrome compared to the general population. In the first year of life, the rate difference in mortality was more pronounced than in childhood and adolescence, suggesting the first year of life being critical for long term survival of people with Down syndrome.

Interestingly, adjusting for patient complexity (measured by the number of diagnoses) and the diagnosis of congenital heart disease mitigated the differences in mortality rates across all age groups. Specifically, when combined with age, sex, hospital type, and department type, these adjustments eliminated any differences in mortality rates for the 0–12 months age group. This highlights the critical role of both patient complexity and congenital heart disease as significant contributors to in-hospital mortality, particularly during the first year of life. Finally, the 30-day readmission rate was also higher in people with Down syndrome throughout life as well compared to the general population. Our findings are consistent with the increased medical complexity demonstrated by the high number of diagnoses associated with Down syndrome from birth.

The limitations of this study must be acknowledged when interpreting the findings. First, the dataset is composed of all medical hospital admissions in Switzerland between 2012 and 2020 and linkage with out-of-hospital data was not feasible for regulatory reasons. Second, we cannot exclude a certain risk of misclassification and underreporting since administrative data were used in our analyses and we were not able to ascertain the diagnoses. Additionally, all hospitalization rates are calculated with the denominator of population life years with no stratification for the diagnosis of Down syndrome (see Methods). Therefore, our dataset allows to compare the trends of hospitalization rates between people with versus without Down syndrome (no comparison of absolute numbers). Due to lower life expectancy of individuals with Down syndrome, hospitalization rates from age 50 years and upwards are smaller in the group of people with Down syndrome compared to the general population. Clinical parameters, including physiognomic features, and laboratory findings were not available as well in the dataset. Furthermore, the distribution of race and ethnicity is not available in the dataset due to regulatory reasons.

In summary, the results discussed in this manuscript offer a comprehensive overview about the age-specific health problems of people with Down syndrome to general practitioners and all medical personnel caring for people with Down syndrome. The results highlight the medical complexity of hospitalized people with Down syndrome and suggest room for improvement in in-hospital outcomes. As the life-expectancy of people with Down syndrome will most likely continue to increase, a comprehensive approach across all age and disease groups will be paramount to ensure that people with Down syndrome receive the required care. We suggest general practitioners and other clinicians to consider our figures to enhance awareness and understanding of the overall complexity and specific morbidities of hospitalized people with Down syndrome, and thereby anticipate emergency hospitalizations across age groups for people with Down syndrome.

Contributors

FE, AK, and GS designed the study. PG analyzed the data and wrote the manuscript with substantial input and supervision from FE, AK and GS. PG and AK have directly accessed and verified the underlying data. All authors were responsible for the decision to submit the manuscript, gave substantial comments on drafts, and approved the final report.

Data sharing statement

The data analyzed in this study is subject to the following licenses/restrictions: The data that support the findings of this study are available from the Swiss Federal Office for Statistics. Restrictions apply to the availability of these data, which were used under license for this study. Requests to access these datasets should be directed to Swiss Federal Office for Statistics.

Declaration of interests

The authors have nothing to disclose.

Acknowledgements

We thank the Swiss Federal Office for Statistics (Bundesamt für Statistik, Neuchâtel, Switzerland) for the acquisition and provision of data.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103062.

References

1 Baksh RA, Pape SE, Chan LF, Aslam AA, Gulliford MC, Strydom A. Multiple morbidity across the lifespan in people with Down syndrome or intellectual disabilities: a population-based cohort study using electronic health records. *Lancet Public Health*. 2023;8(6):e453–e462.
2 Zhu JL, Hasle H, Correa A, et al. Hospitalizations among people with Down syndrome: a nationwide population-based study in Denmark. *Am J Med Genet A*. 2013;161a(4):650–657.
3 Tuppin P, Barthelemy P, Debeugny G, Rachas A. A French nationwide study compared various conditions and healthcare use of individuals < 65 years with a Down's syndrome to those without. *Sci Rep*. 2023;13(1):21865.
4 Down JL. Observations on an ethnic classification of idiots. 1866. *Ment Retard*. 1995;33(1):54–56.
5 de Graaf G, Buckley F, Skotko BG. Estimates of the live births, natural losses, and elective terminations with Down syndrome in the United States. *Am J Med Genet A*. 2015;167a(4):756–767.
6 de Graaf G, Buckley F, Skotko BG. Estimation of the number of people with Down syndrome in the United States. *Genet Med*. 2017;19(4):439–447.
7 John ST, Gayathri K, Sahasranam KV. Cytogenetic patterns, congenital heart disease, and thyroid dysfunction in children with down syndrome. *J Pediatr*. 2022;245:196–200.
8 Mutton D, Alberman E, Hook EB. Cytogenetic and epidemiological findings in down syndrome, england and Wales 1989 to 1993. National down syndrome cytogenetic register and the association of clinical cytogeneticists. *J Med Genet*. 1996;33(5):387–394.
9 Freeman SB, Taft LF, Dooley KJ, et al. Population-based study of congenital heart defects in Down syndrome. *Am J Med Genet*. 1998;80(3):213–217.
10 Santoro SL, Steffensen EH. Congenital heart disease in Down syndrome – a review of temporal changes. *J Congenital Cardiol*. 2021;5(1):1.
11 Versacci P, Di Carlo D, Digilio MC, Marino B. Cardiovascular disease in Down syndrome. *Curr Opin Pediatr*. 2018;30(5):616–622.
12 Liu S, Joseph KS, Lisonkova S, et al. Association between maternal chronic conditions and congenital heart defects: a population-based cohort study. *Circulation*. 2013;128(6):583–589.
13 Khoshnood B, Lelong N, Houyel L, et al. Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: a population-based study. *Heart*. 2012;98(22):1667–1673.

14 Ishikawa T, Iwashima S, Ohishi A, Nakagawa Y, Ohzeki T. Prevalence of congenital heart disease assessed by echocardiography in 2067 consecutive newborns. *Acta Paediatr*. 2011;100(8):e55–e60.
15 Bush D, Galambos C, Ivy DD, Abman SH, Wolter-Warmerdam K, Hickey F. Clinical characteristics and risk factors for developing pulmonary hypertension in children with down syndrome. *J Pediatr*. 2018;202:212–219.e2.
16 Fabia J, Drolette M. Malformations and leukemia in children with Down's syndrome. *Pediatrics*. 1970;45(1):60–70.
17 Cj E. Down syndrome (trisomy 21). In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic basis of inherited disease*. 7th ed. New York, United States: McGraw Hill Inc; 1995 1995.
18 Lott IT, Dierssen M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. *Lancet Neurol*. 2010;9(6):623–633.
19 Kumada T, Ito M, Miyajima T, et al. Multi-institutional study on the correlation between chromosomal abnormalities and epilepsy. *Brain Dev*. 2005;27(2):127–134.
20 Altuna M, Giménez S, Fortea J. Epilepsy in down syndrome: a highly prevalent comorbidity. *J Clin Med*. 2021;10(13).
21 Videla L, Benejam B, Pegueroles J, et al. Longitudinal clinical and cognitive changes along the alzheimer disease continuum in down syndrome. *JAMA Netw Open*. 2022;5(8):e2225573.
22 Selikowitz M. Health problems and health checks in school-aged children with Down syndrome. *J Paediatr Child Health*. 1992;28(5):383–386.
23 Hasle H. Pattern of malignant disorders in individuals with Down's syndrome. *Lancet Oncol*. 2001;2(7):429–436.
24 Lange B. The management of neoplastic disorders of haematopoiesis in children with Down's syndrome. *Br J Haematol*. 2000;110(3):512–524.
25 Motegi N, Yamaoka Y, Moriichi A, Morisaki N. Causes of death in patients with Down syndrome in 2014-2016: a population study in Japan. *Am J Med Genet A*. 2022;188(1):224–236.
26 Strauss D, Eyman RK. Mortality of people with mental retardation in California with and without Down syndrome, 1986-1991. *Am J Ment Retard*. 1996;100(6):643–653.
27 Wu Y, Li J, Qiao J, et al. Effects of traditional Chinese medicine five-element music therapy combined with mirtazapine on depression and limb function recovery after ischemic stroke. *Altern Ther Health Med*. 2023;30(9):210–213.
28 Englund A, Jonsson B, Zander CS, Gustafsson J, Annerén G. Changes in mortality and causes of death in the Swedish Down syndrome population. *Am J Med Genet A*. 2013;161a(4):642–649.
29 Kucik JE, Shin M, Siffel C, Marengo L, Correa A. Trends in survival among children with Down syndrome in 10 regions of the United States. *Pediatrics*. 2013;131(1):e27–e36.
30 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12(12):1495–1499.
31 Fitzgerald P, Leonard H, Pikora TJ, Bourke J, Hammond G. Hospital admissions in children with down syndrome: experience of a population-based cohort followed from birth. *PLoS One*. 2013;8(8):e70401.
32 Hughes-McCormack LA, McGowan R, Pell JP, et al. Birth incidence, deaths and hospitalisations of children and young people with Down syndrome, 1990-2015: birth cohort study. *BMJ Open*. 2020;10(4):e033770.
33 Glinianaia SV, Morris JK, Best KE, et al. Long-term survival of children born with congenital anomalies: a systematic review and meta-analysis of population-based studies. *PLoS Med*. 2020;17(9):e1003356.
34 Glasson EJ, Sullivan SG, Hussain R, Petterson BA, Montgomery PD, Bittles AH. The changing survival profile of people with Down's syndrome: implications for genetic counselling. *Clin Genet*. 2002;62(5):390–393.
35 De Pietro C, Camenzind P, Sturny I, et al. Switzerland: health system review. *Health Syst Transit*. 2015;17(4):1–288. xix.
36 Bull MJ. Down syndrome. *N Engl J Med*. 2020;382(24):2344–2352.
37 Tsou AY, Bulova P, Capone G, et al. Medical care of adults with down syndrome: a clinical guideline. *JAMA*. 2020;324(15):1543–1556.
38 Tenenbaum A, Hanna RN, Averbuch D, Wexler ID, Chavkin M, Merrick J. Hospitalization of children with down syndrome. *Front Public Health*. 2014;2:22.
39 Esperanza RA, Evans A, Tucker D, Paranjothy S, Hurt L. Hospital admissions in infants with Down syndrome: a record-linked population-based cohort study in Wales. *J Intellect Disabil Res*. 2022;66(3):225–239.
40 Karlsson B, Gustafsson J, Hedov G, Ivarsson SA, Annerén G. Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity. *Arch Dis Child*. 1998;79(3):242–245.
41 Van Goor JC, Massa GG, Hirasing R. Increased incidence and prevalence of diabetes mellitus in Down's syndrome. *Arch Dis Child*. 1997;77(2):186.
42 Whooten R, Schmitt J, Schwartz A. Endocrine manifestations of Down syndrome. *Curr Opin Endocrinol Diabetes Obes*. 2018;25(1):61–66.
43 Johannisson R, Gropp A, Winking H, Coerdt W, Rehder H, Schwinger E. Down's syndrome in the male. Reproductive pathology and meiotic studies. *Hum Genet*. 1983;63(2):132–138.
44 Bovicelli L, Orsini LF, Rizzo N, Montacuti V, Bacchetta M. Reproduction in down syndrome. *Obstet Gynecol*. 1982;59(6 Suppl):13s–17s.
45 Urhoj SK, Tan J, Morris JK, et al. Hospital length of stay among children with and without congenital anomalies across 11 European regions-A population-based data linkage study. *PLoS One*. 2022;17(7):e0269874.