All-cause mortality and death by aortic dissection in women with Turner syndrome: A national clinical cohort study

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ABSTRACT

Background Turner syndrome (TS) is a complex genetic disorder with raised mortality. Our objective was to investigate mortality and causes of death in TS.

Methods A matched retrospective observational study of women with TS recruited from the Turner centers in Sweden were conducted. A total of 472 women with TS, ≥16 years old with a cytogenetically verified diagnosis and 2357 controls, matched for birthyear and sex, were examined and followed since 1995 for up to 26 years. Survival analyses were performed with Cox proportional hazard models. Kaplan-Meier curves were generated. Cumulative incidence rates were evaluated by competing risks analysis, using cumulative incidence function.

Results During a mean follow-up of 17 years, 35 (7.4%) women with TS and 70 (3.0%) controls died. All-cause mortality was elevated in TS, hazard ratio (HR) 2.90 (95% CI 1.92-4.37), mainly due to circulatory diseases and notably aortic dissection, with HR of 9.11 (95% CI 4.54-18.25) and 21.79 (95% CI 4.62-102.82), respectively. Aortic dissection was the single largest cause of death in TS, accounting for 23% (8/35) of total deaths. Death by cancer or external causes were not raised in TS. In individuals below 45 years of age death, aortic dissections were greatly increased compared to controls, HR 55.59 (95% CI 2.33-1325.69). From the ages 46 to 80 years a notably higher risk of dying by heart diseases, aortic dissection excluded, was shown in TS compared to controls HR, 7.7 (2.65-22.36). The median survival time was 8 years shorter in TS compared to controls.

Conclusions The increased mortality in TS was mainly driven by aortic dissections in the young and by heart diseases in the older. Healthcare professionals should prioritize detection and monitoring, with emphasis on cardiovascular diseases. (Am Heart J 2025;281:1–9.)

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Background

Turner syndrome (TS) is a complex genetic disorder that affects 1/2000-2500 live birth girls and is caused by a complete or partial absence of 1 sex chromosome.[1]

The clinical features in TS are highly variable but the classical phenotype is characterized by short stature, ovarian insufficiency, and congenital cardiovascular malformations such as bicuspid aortic valve (BAV) and coarctation of the aorta (CoA).[2]

The knowledge about life expectancy in women with TS is limited, bur in 1 study the authors reported a reduced life expectancy with the difference as high as 12.5 years compared to the general population.[3]

Registry studies from Denmark and from Great Britain have also found that mortality in TS is about 3 times higher than the general population, and that mortality is raised for almost all major causes of death and especially for the karyotype 45,X.[4-6] The leading cause of death is diseases of the cardiovascular system with aortic dissection being 1 of the main contributing factors in adults, although death from aortic valve disease is also common among these women.[5,7] In order to offer adequate, up-to date surveillance it is important to broaden the knowledge of mortality and causes of death in TS from contemporary populations. A cohort of 472 adult Swedish women with cytogenetically verified TS, consecutively included and followed for up to 26 years was therefore studied, and mortality and causes of death were compared with 2357 age- and sex-matched controls without TS from the general population.

Materials and methods

This is a matched, retrospective, observational cohort study of adult women with TS, n=472. The patients were consecutively included and followed from January 1, 1995 to December 31, 2020 or to the date of death or emigration, (2 women emigrated from Sweden), whichever occurred first, resulting in a follow-up period of a maximum of 26 years. All participants were recruited from the outpatient clinics i.e., Turner centers in Stockholm, Gothenburg, Linköping, Örebro, Malmö and Uppsala, where they were followed every 5th year by an endocrinologist and gynecologist and at least every 5th year with transthoracic echocardiography (TTE) according to the applicable national and international guidelines for patients with TS at the time of the study period.[8-10] The patients with risk factors for aortic dissection were followed at outpatient clinics for grown-ups with congenital heart diseases. If there were uncertainties or signs at the initial TTE of BAV, CoA, or aortic dilatation, magnetic resonance imaging, MRI was conducted. TTE or MRI are the recommended devises for longitudinal evaluation of the aortic size according to the guidelines.[11,12]

The inclusion criteria were women with cytogenetically verified TS, ≥16 years of age. All ethnicities were included, although the cohort mainly consisted of Caucasian women. Clinical, genetic, and imaging data were collected from the medical records, which included the imaging report with measurements of the aorta and assessments of the valves.

The causes of death were obtained from the medical records and from the National Cause of Death Register. Death by all types of aortic dissection/ ruptured aneurysm (thoracic, abdominal, thoracoabdominal or unspecified site) were included. All patients provided informed consent.

The control group, n=2357, was randomly generated from the Total Population Register obtained from the Statistics Sweden and linked to the National Cause of Death Register, which was used to identify the causes of death. The National Cause of Death Register contains International Classification of Diseases (ICD) codes of all deaths of Swedish citizens permanently living in Sweden, even those that occurred abroad.[13] The proportion of valid diagnoses in the National Patient Register is considered high in patients with cardiovascular disease.[14] The ICD-9 (year 1987-1996) and ICD-10 (year 1997 and onwards) coding systems were used. The different disease groups analyzed in the present study were defined according to the ICD codes and shown in Table 1. Five controls per patient were identified. All control subjects were sampled so that they matched with the patients with TS based on sex and birth year. None had a diagnosis of TS, and all were alive at the time when their matched TS patient was included in the study.

TTE was performed in all women with TS. Death rates per 10 000 person years were calculated by dividing the number of events by the total follow-up time for the studied group. A similar cutoff to the 1 used by Schoemaker et al.[5] was set at 45 years for the age-related subgroup analyses. This age is commonly considered the beginning of "middle age," and therefore, the women were categorized into "younger" and "older" groups accordingly.

The study was approved by the Regional Ethical Review Board in Gothenburg and the Swedish Ethical Review authority (Dnr 2023-04902-02), and performed in accordance with the Helsinki declaration.[15] The study was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement (ALFGBG-718611), Gothenburg Society of Medicine (GLS-985331 and GLS-985519), the Emelle Foundation and the Swedish Heart-Lung Foundation (HLF 2023-0423, 2022-0421 and 2020-0502).

Statistical analysis

Continuous variables were described with means and standard deviations (SD) or medians and ranges. Survival outcomes were analyzed with time-to-event anal-

Table 1. Cause-specific mortality in Turner syndrome vs controls

ICD-10 code	Cause of death	Turner syndrome (n=472)		Controls (n=2357)		Cause specific Hazard Ratio (95% CI)
		Number of deaths (% of total number)	Deaths per 10000 patient years	Number of deaths (% of total number)	Deaths per 10000 patient years	
A00-B99	Infectious and parasitic diseases	0 (0)		1 (1.4)		
C00-D48	All malignancies	3 (8.6)	1.44	28 (40)	2.67	0.61 (0.18-2.01)
E00-E90	Endocrine, nutritional and metabolic diseases (Diabetes mellitus)	2 (5.7)		2 (2.9)		
F00-F99	Mental and behavioral disorders (Dementia)	0 (0)		2 (2.9)		
G00-G99	Diseases of the nervous system	0 (0)		2 (2.9)		
I00-I99	Diseases of the circulatory system	21 (60)	10.06	14 (20)	1.33	9.11‡ (4.54-18.25)
I20-I25	Ischemic heart diseases	3 (8.6)		5 (7.1)		1.44 (0.46-4.46)
I30-I49	Endocarditis, cardiac arrest, Atrial fibrillation and atrial flutter, cardiomyopathy	4 (11.4)		1 (1.4)		
I50.0-I51.7, 4289*	Heart failure	3 (8.6)		1(1.4)		
I60-I69+I70.9	Cerebrovascular diseases	3 (8.6)		5 (7.1)		1.44 (0.46-4.46)
I71.0-I71.9	Aortic aneurysm (ruptured) and dissection	8 (22.9)	3.83	2 (2.9)	0.19	21.79 ‡ (4.62-102.82)
J00-J99	Diseases of the respiratory system	2 (5.7)		1 (1.4)		
K00-K93, 705*	Diseases of the digestive system	2 (5.7)		2 (2.9)		
M00-M99	Diseases of the musculoskeletal system and connective tissue	0 (0)		2 (2.9)		
N00-N99	Diseases of the genitourinary system	0 (0)		1 (1.4)		
R99	Unknown cause of death	1 (2.9)		1 (1.4)		
V01-Y98 9290* 9550*	External causes of mortality (accidents and violence)	4 (11.8)	1.92	14 (20)	1.24	1.69 (0.55-5.20)
	All causes of death	35	16.77†	70	6.66†	2.90‡ (1.92-4.37)

* ICD-9
† Crude mortality rate
‡ $P < .0001$.

ysis methods. The overall survival for women with TS vs. population-based controls was analyzed using Kaplan-Meier survival curves and compared using the log rank test. Risk factors for all-cause mortality in women with TS was analyzed using Cox proportional hazards regression, unadjusted and adjusted for age at inclusion. Firth's penalized maximum likelihood estimation was applied to minimize bias in parameters with low numbers. Corresponding hazard ratios (HR) are presented with 95% confidence intervals (CIs). The cumulative incidence of death by aortic dissection, other circulatory system diseases, cancer, and violence or accident was estimated using cumulative incidence functions, accounting for competing events (i.e., death by other causes). Cause-specific Cox regression analysis (i.e., with censoring at a competing event) was used to evaluate risk of death by aortic dissection, other circulatory system diseases, cancer, and violence or accident in women with TS compared to population-based controls.

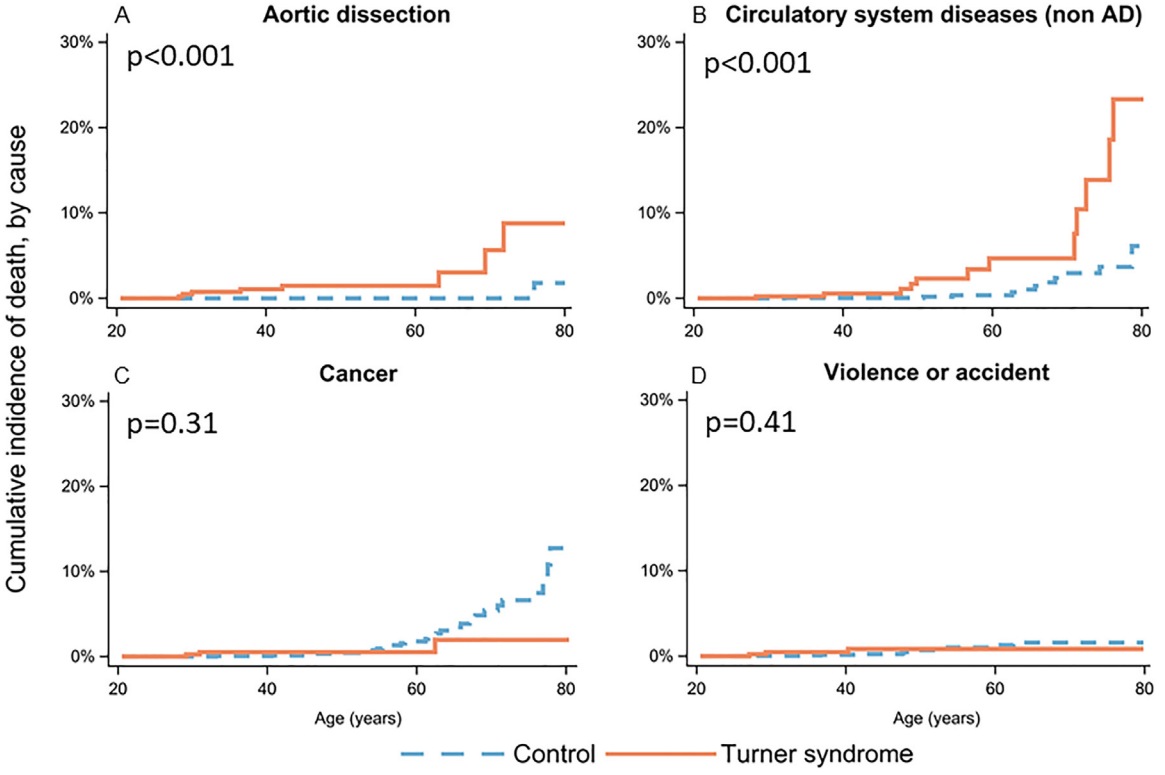
All analyses were performed using either SPSS version 24.0 for Windows (IBM, Armonk, NY, USA) or SAS version 9.4 (SAS Institute Inc., Cary, NC USA).

Results

Mortality in TS compared to controls

The all-cause mortality was higher in TS compared to the control group, HR 2.90 (1.92-4.37), $P < .0001$. Details on the number and causes of death for both TS and controls are summarized in Table 1. Specifically, deaths related to circulatory system diseases of all causes, and notably aortic dissection, showed significantly higher HR: 9.11 (4.54-18.25) and 21.79 (4.62-102.82) respectively, with *P*-values of < .0001. After excluding aortic

Figure 1. Title: Cumulative risk of death in TS vs controls. **Legend:** The cumulative risk of death from (A) aortic dissection, (B) diseases of the cardiovascular system (i.e. ischemic heart diseases, endocarditis, cardiac arrest, atrial fibrillation and atrial flutter, cardiomyopathy, heart failure, cerebrovascular diseases), (C) cancer and (D) external causes (accidents and violence) in women with Turner syndrome vs population-based controls. AD, aortic dissection.



dissections, TS still exhibited increased all-cause mortality with an HR of 2.3 (1.47-3.62), $P = .0003$. Subgroup analyses revealed that the risk of all-cause mortality under the age of 45 was significantly higher in TS than in controls, HR 5.52 (2.44-12.51) $P < .0001$, mainly driven by aortic dissections HR 55.59 (2.33-1325.69) $P = .013$. The mortality by circulatory diseases (excluding aortic dissection) did not differ significantly between TS and controls ($P = .057$) before the age of 45. From ages 46 to 80 years, a notably higher risk of dying by heart diseases (ischemic heart diseases, endocarditis, cardiac arrest, atrial fibrillation and atrial flutter, cardiomyopathy, and heart failure), was shown in TS compared to controls HR, 7.7 (2.65-22.36) $P = .0002$.

On the contrary, death by cancer or external causes (accidents and violence) did not differ in TS compared to the control group. The HR for cancer in TS vs controls was 0.61 (0.18-2.01), $P = .41$. No women with TS died of breast cancer or by cancer of the female genital organs (ICD-10 C51-58), while 4 women died of breast cancer, 1 of uterus cancer, and 2 of ovary cancer in the control group. For external causes (accidents and violence) HR in TS vs control was 1.69 (0.55-5.20), $P = .36$. No cases of congenital malformations were recorded as the cause of death, neither in the TS group nor in the control group. Monosomy was not associated with increased mortality in TS, HR 1.59 (0.74-3.44), $P = .24$.

Figure 1 illustrates the cumulative incidence rates for different causes of death, comparing TS to controls, with adjustments made for the different causes of death. The cumulative incidence of death due to aortic dissection and diseases of the circulatory system (i.e. ischemic heart diseases, endocarditis, cardiac arrest, atrial fibrillation and atrial flutter, cardiomyopathy, heart failure, cerebrovascular diseases), was increased in women with TS compared to controls.

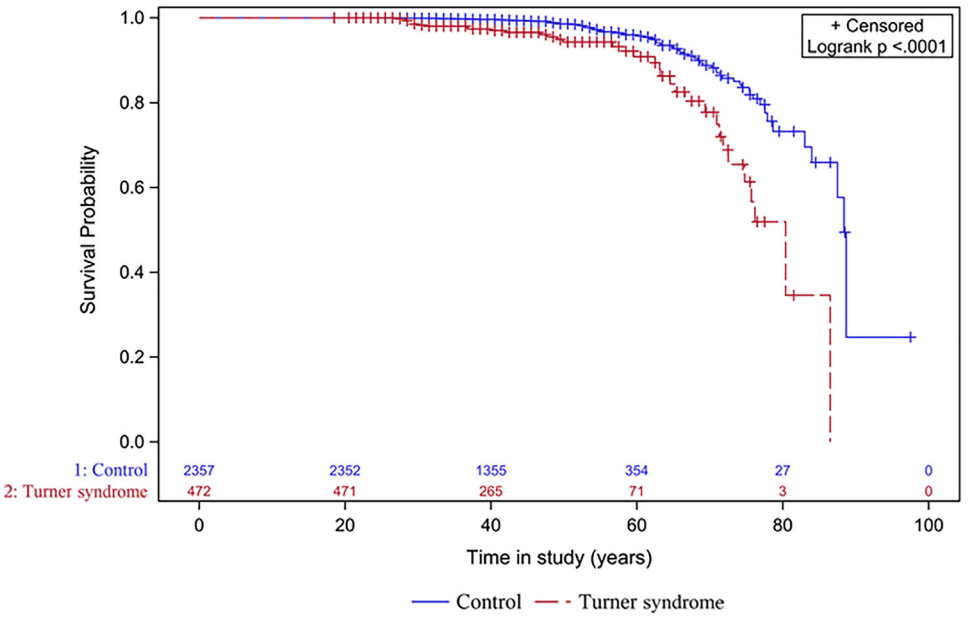
Baseline characteristics in the 472 women with TS who were alive or died during the up to 26 years follow-up are presented in Table 2. In the matched control group consisting of 2360 women without TS 3 were excluded due to death prior to the inclusion date of the patient with TS, resulting in a final control group of 2357 individuals. The mean age at inclusion was 28 (±11.9) years, ranging from 16 to 78 years at inclusion for the women with TS and controls. Over an average follow-up period of 17 years, median 17.5 years (ranging from 1 month to 26 years), 35

Table 2. Clinical characteristics in 472 women with Turner syndrome at inclusion

	Women with TS Mean±SD	Number*
Age, years	28.2±11.9	472
Height, cm	153.6±7.1	471
Body mass index, kg/m^2	25.2±4.6	471
Monosomy (45,X), n (%)	268 (56.8)	472
Aortic coarctation, n (%)	45 (10.4)	434†
Bicuspid aortic valve, n (%)	97 (22.4)	434†
First Aortic size index, cm/m^2	1.81±0.33	409†
Systolic blood pressure, mmHg	123.3±15.1	458
Diastolic blood pressure, mmHg	76.8±9.5	458
Previously given growth hormone therapy, n (%)	249 (53.2)	468
Ongoing estrogen hormone replacement therapy, n (%)	388 (85.3)	455
Blood pressure medication, n (%)	71 (16.0)	445
Total cholesterol, mmol/L	4.91±1.06	439
Smoker, n (%)	28 (6.0)	466
Diabetes mellitus, n (%)	22 (4.9)	450

* available measurements.
† all patients had undergone echocardiography, but assessments of the valves/aortic measurements were not available in all the reports from the 1990s or early 2000s.

Figure 2. Title: Kaplan-Meier survival curves in Turner syndrome vs controls. **Legend:** Kaplan-Meier curve comparing survival between women with Turner syndrome (red dashed line) vs population-based controls (blue solid line).

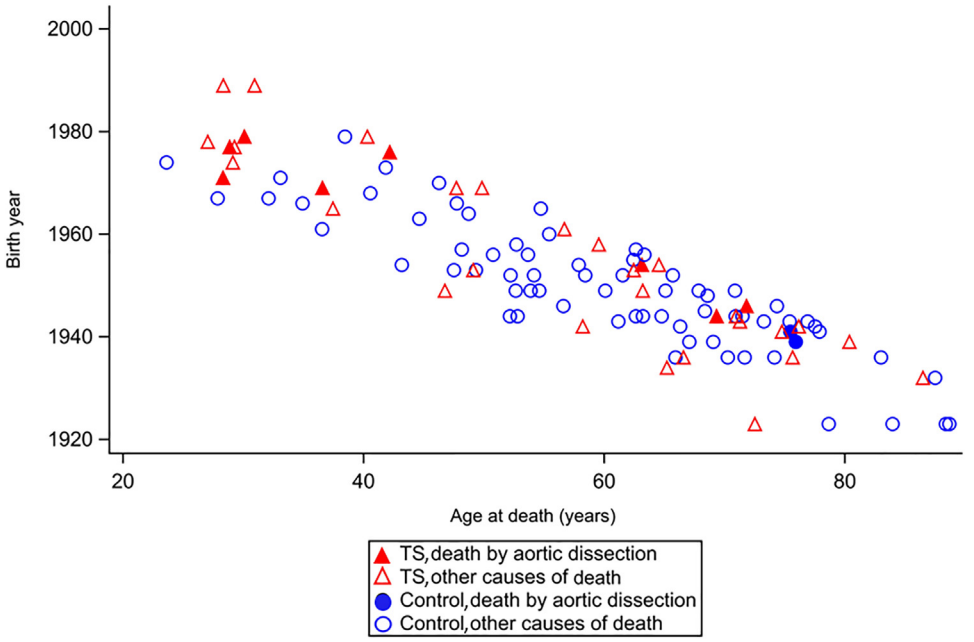


(7.4%) women with TS and 70 (3.0%) women in the control group died, respectively. Kaplan Meier curves representing all-cause mortality rates in both TS and controls are illustrated in Figure 2. The estimated median survival time was 80.4 years (70.9-86.5) for TS and 88.4 (78.7-88.7) for the controls, respectively.

Aortic dissection

During the follow-up period, 5/472 women with TS (1.1%) underwent prophylactic aortic surgery due to aortic aneurysm, and 20/472 (4.2%) women with TS experienced aortic dissection/ruptured aortic aneurysm. Eight of the 20 (40%) women who experienced aortic dissection died, Supplementary Table 1. One of those who died had undergone acute aortic surgery. Two women among the controls (2/2357; 0.08%) suffered fatal aortic dissection. The 8 women with TS who died from aortic dissection were considerably younger, as depicted in Figure 3, compared to the controls. Among the women with TS who died before the age of 45, 5 out of 12 (42%) deaths

Figure 3. Title: Death by aortic dissection in women with Turner syndrome and controls. **Legend:** Death by aortic dissection vs other causes in relation to age in 35 women with Turner syndrome and 70 population-based controls.



were attributed to aortic dissection. The mean age for all women who suffered from aortic dissection was 41 (±14.9) years spanning from 16 to 71 years and 38.1 (±11.6) years in those who survived the dissection. A diverse range of TS karyotypes was present, with the majority, 13/20 (65%), characterized by monosomy (45,X). As seen in Supplementary Table 1, the aortic dissections occurred evenly distributed since the 1990s with no tendency to decline. The 2 women who experienced aortic dissection during pregnancy survived.

Discussion

Mortality in TS compared to controls

This large nationwide observational study in women with TS with matched controls demonstrated a 3-fold increased mortality. This was mainly explained by cardiovascular disease. Death by aortic dissection demonstrated a 22-fold increased risk in TS during the up to 26 years follow-up.

Aortic dissection was the main cause of death in women with TS below 45 years of age. The women with TS were regularly checked, >50% of all received growth hormone (90% of the young), the majority with ongoing estrogen replacement therapy and well-regulated blood pressure and lipids. The aortic dissections occurred in spite of examinations according to updated international guidelines.[1,16,17] While the number of deaths in absolute terms was low in TS, it stands as relatively high when compared with the control group. In women with TS >45 years of age death by heart diseases, (cerebrovascular diseases and aortic dissections excluded), were increased compared to controls, which is in line with previous research by Schoemaker et al.[5] using a similar cut-off of age.

The mortality rate from cancer did not differ in TS compared to the control group. This aligns with previous findings.[4,5,18,19]

Deaths resulting from external causes (accidents and violence) were heterogenous, spanning from car accidents, exposure to fire, poisoning of undetermined intent to suicide. There are few studies in TS reporting on mortality due to external causes compared to the general population: Schoemaker et al.[5] found a significant increase, Standardized mortality ratio (SMR) 2.2 (95% CI 1.3-3.6), in contrast to Swerdlow et al.[19] RR 1.5 (95% CI 0.18-5.46). In this study, mortality from external causes was not more frequent in women with TS compared to the control group. This observation might be explained by the notion that the quality of life and in TS has been found to be comparable to that of women in the general population in Sweden.[20]

In TS, the cumulative risk of death due to circulatory system diseases (excluding aortic dissection) represents the highest incidence rate at age 80 as seen in Figure 1. This pattern corresponds with Schoemaker et al.'s findings, where their TS cohort exhibited the highest absolute excess risk for circulatory system diseases, reaching a cumulative risk of 34% for death due to these conditions by the age of 85.[5]

Aortic dissection

In clinical practice, TTE is the most commonly used technique for assessing the proximal aorta and the aortic valve. While MRI is excellent for measuring aortic diameters, it is a costly option. Access to MRI has increased over time, and in Sweden it is conducted when TTE results are inconclusive. In cases with aortic dilatation, measurements are confirmed with Computed tomography (CT)/MRI, and decisions of prophylactic surgery are always based on measurements from these modalities.

Hypertension, BAV, CoA (even after surgical repair), rapid aortic growth and pregnancy are all known risk factors for aortic dissection.[11] Other commonly established risk factors for cardiovascular disease were not more prevalent in the women with TS in this study (smoking, diabetes mellitus, and blood lipid levels) than in the female population in Sweden previously described by Krantz et al.[20] In order to improve rapidity of urgent management an alert pocket card to inform the emergency personnel about the higher risk of aortic dissection in TS, has recently been developed by Calanchini et al.[21] in collaboration with the TS Support Society. This invention might also be lifesaving.

In the present study 40% (8/20) of the aortic dissections were fatal. Among those who died, 1 had undergone acute aortic surgery. Harris et al.[22] showed in a contemporary population that the mortality by type A acute aortic dissection was 0.5% for each hour after the dissection occurred in patients who were medically managed, leading to a 48-hour mortality of 23.7 %. In patients who received surgery the 48-hour mortality was 4.4%. This shows how important early detection and rapid surgery are for survival.[22]

The average age at the time of the event was 41 years, in line with previous published literature with a mean age between 30 and 49 in TS and 71 years in women in the general population, respectively.[23-27] In this study, the vast majority of the aortic dissections in the women with TS were located in the ascending aorta, which is in accordance with findings by Yetman et al.[26,28] Unfortunately, the information about the location was not available in the 2 controls who suffered a dissection, who both were coded as I71.0 (dissection of aorta, any part). The cumulative incidence rate of fatal aortic dissection in TS was approximately 10% by the age of 80 (Figure 1), but this should be interpreted with caution as the number of women with TS who died was small and the cohort was relatively young.

Strengths and limitations

The novelty of this large nationwide, and well examined cohort was the updated HR of all-cause mortality in TS and that aortic dissection is still the main cause of death, especially in the young women with TS. Furthermore, despite heightened awareness and recommendations for frequent examinations of the aortic diameter, as well as consideration of surgical preventive interventions for those at highest risk, our study could not show any decrease in the frequency of aortic dissections in individuals with TS over the past 25 years. Another new finding was that monosomy was not associated with increased mortality in TS.

The studied group represents approximately 2/3 of the patients >16 years with a diagnosis of TS in Sweden. The follow-up period for the women with TS was long and standardized and they were compared to an age- and sex-matched control group.

As with all multicenter studies, aortic diameters were measured at different centers, introducing potential measurement errors. Different TTE devices were used, and it remains uncertain whether all measurements were consistently performed at the same anatomical location (e.g., at the level of the right pulmonary artery). This inconsistency could impact the results, as the size of the ascending aorta can vary significantly depending on the measurement site. Additionally, intra- and interobserver variability in aortic diameter measurements may further influence the accuracy of the findings. Therefore, measurements of the ascending aorta in Supplementary Table 1 should be interpreted with caution.

Girls with TS <16 years of age were not studied. Hence, survivors of those with the most severe cardiac malformations were probably not included in this adult cohort, as indicated by the absence of deaths due to congenital malformations, which are otherwise elevated in TS.[4,5,19] This could lead to survival bias which might result in reduced all-cause mortality rate if generalizing the results to all ages.

The prevalence of monosomy was relatively high in his study (57%) compared to studies on mortality in TS by Shoemaker et al.,[5] and Stochholm et al.,[4] (36 and 45%, respectively). This might lead to ascertainment bias, as monosomy is associated with a more severe phenotype and a higher mortality rate.[6] However, it is possible that the 12% difference in the prevalence between our study and the study by Stochholm et al. plays a minor role overall, as the studies by Schoemaker et al. and Stochholm et al. reported the same increase in mortality despite a 9% difference in the prevalence of monosomy between their studies. The lack of a significant association between monosomy and aortic dissection in this study underscores this conclusion.

The TS population was also relatively young and, consequently, the number of deaths low, resulting in great confidence intervals. Nevertheless, the results align with previous reports on mortality rates in TS.[5,7,19]

Conclusions

Aortic dissection was the main cause of death in Swedish women with Turner syndrome below 45 years of age who had survived childhood. The all-cause mor-

tality rate in women with TS was 3 times higher than in women in the general population, mainly driven by aortic dissection among the younger individuals and by heart diseases among the older.

Healthcare professionals monitoring patients with TS should prioritize cardiovascular surveillance, and encourage women with TS to carry an alert pocket card to inform the emergency staff about their increased risk of aortic dissection.

Data availability

Datasets analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest and are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

CRediT authorship contribution statement

Sofia Thunström: Writing – original draft, Data curation, Conceptualization. **Erik Thunström:** Writing – original draft, Data curation, Conceptualization. **Sabine Naessén:** Writing – review & editing, Data curation. **Kerstin Berntorp:** Writing – review & editing, Data curation. **Margareta Laczna Kitlinski:** Writing – review & editing. **Bertil Ekman:** Writing – review & editing, Data curation. **Jeanette Wahlberg:** Writing – review & editing, Data curation. **Ingrid Bergström:** Writing – review & editing, Data curation. **Magnus Isaksson:** Writing – review & editing, Data curation. **Carmen Basic:** Writing – review & editing, Data curation. **Teresia Svanvik:** Writing – review & editing, Data curation. **Inger Bryman:** Writing – review & editing, Data curation. **Kerstin Landin-Wilhelmsen:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2024.11.007.

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