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Age-related cardiovascular disease in Down syndrome: A population-based matched cohort study

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Background. Life expectancy for individuals with Down syndrome (DS) has increased dramatically. To improve detection and prevention, the risk of age-related cardiovascular disease in this population needs to be better defined.

Methods. We performed a population-based matched cohort study. Through the National Patient Register (NPR) and/or the Medical Birth Register, we identified all individuals born in Sweden between 1946 and 2000 with a diagnosis of DS. Each individual with DS was matched to 50 comparators by sex, birth year, and county of birth. Data on ischemic and hemorrhagic stroke, acute myocardial infarction (AMI), and covariates indicating cardiovascular risk were retrieved from the NPR. Associations between DS and cardiovascular outcomes were estimated using Cox proportional hazards models. We also assessed the influence of cardiovascular risk factors.

Results. We included 5155 individuals with DS, of which 55% were male. The median age at the end of follow-up was 35 in the DS population and 42 among the comparisons. DS was associated with increased risk of ischemic stroke (hazard ratios [HR] 4.41, 95% confidence intervals [CI] 3.53–5.52) and hemorrhagic stroke (HR 5.14, 95% CI 3.84–6.89). The overall risk of AMI was similar in DS and comparators but increased in young individuals with DS. The risk of ischemic stroke was elevated in individuals with DS with selected atherosclerotic (HR 12.67, 95% CI 7.04–22.78) as well as embolic (HR 10.35, 95% CI 6.69–16.01) risk factors, as compared to comparators without risk factors.

Conclusion. Individuals with DS were at increased risk of cardiovascular outcomes.

Keywords: cardiovascular disease, cerebral hemorrhage, cerebral infarction, down syndrome, myocardial infarction

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; DS, Down syndrome; HR, hazard ratio; ICD, International Classification of Diseases; MBR, Medical Birth Register; NPR, National Patient Register

Annie Pedersen and Anna Skarin Nordenvall contributed equally to this work.

Introduction

Down syndrome (DS), caused by a partial or complete triplication of chromosome 21, is the most frequent survivable autosomal aneuploidy and the most common genetic cause of intellectual disability in the world [1, 2]. Over the last decades, the life expectancy for individuals with DS has increased dramatically from 25 years in 1983 [3] to 60 years in 2020 [4]. This development entails age-related comorbidities in these individuals that, due to their different genetic constitution, do not seem to mirror those of a general aging population [5–8]. Therefore, there is a need for large population-based studies on aging DS individuals to improve

detection, prevention, and treatment of age-related comorbidities in this unique population.

The extra chromosome 21 in DS results in a diversity of manifestations from early childhood, including congenital heart defects and intellectual disability, as well as an increased risk for autoimmune and hematological disorders, including leukemia [8, 9], and, later in life, early-onset Alzheimer's disease [8, 10]. Chromosome 21 includes a large number of protein-coding and non-protein-coding genes, and the exact molecular mechanisms underlying the phenotypic manifestations of DS are not well-known [9]. However, at least in part, it is thought to result from the overexpression, including its downstream consequences, of specific genes on chromosome 21 [9]. For instance, overexpression of the *APP* gene is considered one of the main causes of Alzheimer's disease, and the genes *RCAN1* and *DYRK1A* have been suggested to play a role in cardiovascular prevention [7, 11]. Clearly, experimental studies are needed to further elucidate the pathophysiological mechanisms underlying the different phenotypic manifestations of DS. These studies need to be complemented by robust observational data to define the DS phenotype across a lifespan.

To date, the number of population-based studies on age-related comorbidities in large cohorts of DS is limited. Clinical practice guidelines for this group are hampered by the lack of high-quality evidence, which limits the strength of recommendations and highlights the need for additional research within this area [12]. Observational data suggest that the distribution of traditional vascular risk factors differs in DS compared to the general population, with a higher prevalence of obesity, sedentary lifestyle, and dyslipidemia, but a remarkably low prevalence of hypertension [7, 8, 13]. In addition, DS individuals are thought to be protected from the development of atherosclerosis [14–16]. Nevertheless, increased risk both for ischemic heart disease and cerebrovascular disease in DS compared to the general population was reported in a recent large meta-analysis [17]. In other cohorts, an increased risk of cerebrovascular events but a lower risk of coronary events has been observed [8, 18]. To conclude, the bodily aging process of individuals with DS differ from that of the general population, but detailed assessment of comorbidities in large population-based cohorts are scarce. Here, we performed a population-based matched cohort study to assess the risk of cardiovascular disease in adult individuals with DS, while taking cardiovascular risk factors into account.

Methods

We used a population-based matched cohort design with data from Swedish national registers to study the associations between DS and selected cardiovascular outcomes. Ethical permission was granted by the Swedish Ethical Review Authority (2018/1849-32).

National registers

Sweden has a long tradition of collecting population-based data on demographics and health in national registers. Linkage between registers is made possible through the personal identification number that is given to all permanent Swedish residents [19]. We collected healthcare data, diagnoses defined using the International Classification of Diseases (ICD) codes, from the National Patient Register (NPR) and the Medical Birth Register (MBR) held by the Swedish National Board of Health and Welfare. The NPR was founded in 1964 and reached nationwide coverage in 1987. It contains data on diagnoses and procedures in inpatient care from 1964 and outpatient specialist care from 2001 [20]. The MBR was established nationwide in 1973 and registers pre- and perinatal data on both mother and child [21]. Further, the Swedish National Board of Health and Welfare holds the Swedish Cause of Death Register from which the date of death was attained [22]. The Total Population Register was used to collect information on place and date of birth, migration, and parental age, whereas parental educational level was obtained from the longitudinal integrated database for health insurance and labor market studies [23, 24].

Exposure and outcomes

Using the NPR and/or MBR we identified all individuals born in Sweden between 1946 and 2000 with a diagnosis of DS (Table S1), that is, starting with individuals who were 18 years of age at the beginning of the follow-up period in 1964. DS individuals were excluded from the study if there was a diagnosis of another chromosomal aberration after the last date of DS diagnosis. Moreover, to minimize misclassification, only individuals with at least two diagnostic events of DS were included. Each DS individual was matched to 50 comparators by sex, birth year, and county of birth using

the Total Population Register. Each DS individual was matched to 50 comparators by sex, birth year, and county of birth using the Total Population Register. Outcomes investigated were stroke, subcategorized as hemorrhagic or ischemic, and acute myocardial infarction (AMI) according to ICD 7–10 (Table S2) until end of follow-up December 31, 2018. Data on cardiovascular outcomes were retrieved from the NPR, and the date of the first diagnostic event was used in analyses.

Covariates

To investigate if the risk of cardiovascular outcomes was even further increased in DS patients with cardiovascular risk factors, three proxy variables were created based on available and reliable variables in the Swedish registers (Table S3). The first variable, indicating cardioembolic risk, included diagnoses of heart malformations and/or arrhythmias. The second variable, indicating atherosclerotic risk, included diabetes, cerebral atherosclerosis, and/or occlusion/stenosis of precerebral arteries. The third variable, describing any cardiovascular risk factor, included all aforementioned diagnoses. As the distribution of traditional vascular risk factors is expected to differ in DS by for instance a high prevalence of heart malformations and a low prevalence of atherosclerosis, we chose to present both the combined proxy variables for cardioembolic and atherosclerotic risk and the single variables heart malformations, arrhythmias and diabetes in the analyses assessing whether the risk of cardiovascular outcomes in individuals with DS was modified by these risk factors. Parental level of education was used as a proxy for socioeconomic status in adjusted models, with data retrieved from the longitudinal integrated database for health insurance and labor market studies, categorized as primary, secondary, and post-secondary educational levels. Parental age at birth was categorized as <30, 30–34, 35–39, and >39.

Statistical analyses

The associations between DS and outcomes were estimated using Cox proportional hazards models, with attained age as the underlying time scale. Individuals were followed from the age of 18 until the outcome event, emigration, death, or the end of the study period (December 31, 2018). Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Models were adjusted for sex, birth year, and birth county through matching and further adjusted for parental age and parental educational level. Models were tested for proportionality using Schoenfeld's residuals and stratified by sex and age when tests indicated non-proportionality. When studying whether the risk of cardiovascular outcomes was modified by the presence of cardiovascular risk factors, we categorized individuals into four groups (non-DS without risk factors, non-DS with risk factors, DS without risk factors, and DS with risk factors), using the non-DS without risk factors as the reference group.

Statistical analyses were not performed if there were less than five events in the DS group, and the number of cases was censored for confidentiality. All statistical analyses were performed using Stata version 16.1.

Results

In total, 5939 individuals born in Sweden 1946–2000 had received a diagnosis of DS in the NPR or MBR. Sixty-three individuals had been diagnosed with another chromosomal aberration after the last date of DS diagnosis and were therefore excluded. Finally, 5155 individuals fulfilled the criteria of a minimum of two diagnostic DS events and were included in further analyses.

The characteristics of the study population are presented in Table 1. Fifty-five percent of the cohort consisted of males. The median age at the end of follow-up was lower in the DS population than among comparators, 35 versus 42 years of age. As expected, the age of the DS individuals' parents was higher than that of comparators, 19.4% of the DS mothers had an age of more than 39 years at birth, as compared to 2.9% of the non-DS mothers. Parental educational level was similar; however, missing for a larger proportion in the DS cohort.

Both hemorrhagic and ischemic strokes were more prevalent in the DS cohort, affecting 3.9% of DS individuals and 1.4% of comparators. The prevalence of registered AMI among DS was low, 0.6%, and only half of that of non-DS individuals, 1.2%. This was further reflected by a low prevalence of open coronary heart procedures in the DS cohort, 0.1%, as compared to 1.4% of comparators. As expected, heart malformations were more prevalent in the DS group, affecting nearly a third of DS individuals. The same was true for diabetes, making the selected presumed embolic and atherosclerotic risk factors more prevalent in DS, 30.6% and

Table 1. *Characteristics of the study population. Prevalence of outcomes and covariates amongst DS and non-DS individuals.*

	DS		Non-DS	
	N	%	*N*	%
Total number of individuals	5155		257,750	
Birth year				
1946–1950	401	7.8	20,050	7.8
1951–1960	848	16.5	42,400	16.5
1961–1970	833	16.2	41,650	16.2
1971–1980	874	17.0	43,700	17.0
1981–1990	997	19.3	49,850	19.3
1991–2000	1202	23.3	60,100	23.3
Sex				
Male	2848	55.2	142,400	55.2
Female	2307	44.8	115,350	44.8
Parental level of education				
Primary	1061	20.6	51,347	19.9
Secondary	1883	36.5	110,146	42.7
Post-secondary	1821	35.3	89,204	34.6
Missing	390	7.6	7053	2.7
Maternal age at birth				
<30	1741	33.8	159,164	61.8
30–34	1164	22.6	62,053	24.1
35–39	1189	23.1	27,461	10.7
>39	1000	19.4	7459	2.9
Missing	61	1.2	1613	0.6
Paternal age at birth				
<30	1235	24.0	110,242	42.8
30–34	1249	24.2	73,345	28.5
35–39	1090	21.1	41,849	16.2
>39	1428	27.7	26,332	10.2
Missing	153	3.0	5982	2.3
Cardiovascular outcomes and covariates				
Non traumatic intracerebral hemorrhage	62	1.2	906	0.4
Subarachnoid hemorrhage	11	0.2	549	0.2
Any hemorrhagic stroke	71	1.4	1354	0.5
Ischemic stroke	121	2.3	2328	0.9
Stroke NOS	21	0.4	286	0.1
Any stroke[a]	199	3.9	3614	1.4
Acute myocardial infarction	32	0.6	3181	1.2
Any coronary artery surgery	5	0.1	3482	1.4
Open coronary artery surgery	<5		795	0.3
Endovascular coronary artery surgery	<5		2921	1.1
Atrial fibrillation or flutter	57	1.1	4615	1.8
Other arrhythmias	9	0.2	534	0.2
Any arrhythmia	65	1.3	4992	1.9
Diabetes mellitus any	272	5.3	8511	3.3
Diabetes mellitus Type II	183	3.5	6475	2.5
Heart malformations	1551	30.1	1741	0.7
Atherosclerosis of cerebral or precerebral arteries	0	0.0	290	0.1
Any cardioembolic risk factor[b]	1575	30.6	6565	2.5
Any atherosclerotic risk factor[c]	272	5.3	8728	3.4
Any cardiovascular risk factor[d]	1792	34.8	14,552	5.6
Age at cardiovascular outcomes				
Median age at ischemic stroke diagnosis (IQR)	44.3 (23.0)		57.2 (14.2)	
Median age at hemorrhagic stroke diagnosis (IQR)	52.3 (16.9)		51.4 (20.5)	
Median age at AMI diagnosis (IQR)	50.0 (21.6)		56.9 (11.9)	
Emigrated	9	0.2	11,276	4.4
Median age at emigration (IQR)	24.3 (10.2)		28.2 (11.8)	
End of follow up, December 31, 2018	3773	73.2	239,561	92.9
Median age at end of follow up (IQR)	34.9 (20.4)		42.4 (28.9)	

Note: For details of included ICD codes, please refer to Tables S2 and S3.
Abbreviations: DS, Down syndrome; IQR, interquartile range; NOS, not otherwise specified.
[a]Including subarachnoid or intracerebral hemorrhage, ischemic stroke, or stroke NOS.
[b]Presence of heart malformations or arrhythmias.
[c]Presence of diabetes, cerebral atherosclerosis, occlusion or stenosis of precerebral arteries.
[d]Presence of heart malformations, arrhythmias, diabetes, cerebral atherosclerosis, or occlusion or stenosis of precerebral arteries.

Table 2. *Cardiovascular outcomes in DS as compared to non-DS.*

	N	aHR (95% CI)
Intracerebral hemorrhage	62	5.03 (3.67–6.88)[a]
Subarachnoid hemorrhage	11	1.20 (0.59–2.44)[a]
Any hemorrhagic stroke[b]	71	5.14 (3.84–6.89)[a]
Ischemic stroke	121	4.41 (3.53–5.52)
Stroke NOS	21	6.30 (3.59–11.06)[a]
Any stroke[c]	199	4.18 (3.50–4.98)[a]
Acute myocardial infarction	32	0.85 (0.56–1.29)
Any coronary artery surgery	5	0.13 (0.05–0.63)[a]

Note: Results from adjusted Cox proportional hazards models showing hazard ratios for cardiovascular outcomes in DS as compared to non-DS. All analyses are adjusted for birth county, parental age and level of education, and sex.
Abbreviations: CI, confidence interval; DS, Down syndrome; HR, hazard ratio; NOS, not otherwise specified
[a]Does not fulfill the proportional hazard assumption and should be interpreted as the average HR over the whole study period.
[b]Including non-traumatic subarachnoid or intracerebral hemorrhage.
[c]Including non-traumatic subarachnoid or intracerebral hemorrhage, ischemic stroke, or stroke NOS.

5.3%, respectively, compared to 2.5% and 3.4% in the comparators.

Results from adjusted Cox regression models are displayed in Table 2. DS was associated with an increased risk of hemorrhagic stroke (HR 5.14, 95% CI 3.84–6.89), ischemic stroke (HR 4.41, 95% CI 3.53–5.52), and any type of stroke (HR 4.18, 95% CI 3.50–4.98), with no significant differences in risk between men and women (Table S4). To compare risk factors for different etiologies of stroke, we performed analyses assessing individuals with selected atherosclerotic and cardioembolic risk factors separately. The risk of stroke was modified by the presence of these risk factors (Table 3). The risk of ischemic stroke was 10 times higher among DS individuals with selected embolic risk factors (HR 10.35, 95% CI 6.69–16.01) as compared to non-DS individuals without risk factors and significantly increased as compared to DS individuals without the selected embolic risk factors (HR 4.24, CI 95% 3.27–5.49). The risk of ischemic stroke in DS individuals without selected embolic risk factors was similar to that of non-DS individuals with selected embolic risk factors (HR 4.33, 95% CI 3.84–4.89). The risk of ischemic stroke was also elevated in DS with the selected atherosclerotic risk factors (HR 12.67, 95% CI 7.04–22.78). The heightened risk of hemorrhagic stroke in DS was not modified by the included cardiovascular risk factors, and it was increased in both individuals with and without selected cardiovascular risk factors (HR 4.66, 95% CI 2.65–8.20 and HR 5.80, 95% CI 4.13–8.15), as compared to non-DS individuals without the selected cardiovascular risk factors. No significant sex differences were observed when comparing DS individuals with and without risk factors (data not shown). The overall risk of AMI was similar among non-DS and DS individuals (HR 0.85, 95% CI 0.56–1.29). However, in younger individuals (<40 years of age), the risk of AMI was increased in DS (HR 3.48, 95% CI 1.55–7.78). Individuals with the selected embolic as well as atherosclerotic risk factors were, however, at increased risk of AMI regardless of having a DS diagnosis or not (Table 3). Notably, despite similar risks of AMI in both DS and non-DS individuals, the likelihood of treatment with coronary heart intervention was lower in DS (HR 0.13, 95% CI 0.05–0.34).

As the prevalence of cardiovascular risk factors as well as primary prevention has changed during the lengthy study period, we performed additional analyses stratified by birth year, that is, for individuals born in 1946–1974 and 1975–2000, respectively. Results are presented in Table S5. In summary, HR was slightly higher for hemorrhagic stroke in the older compared to the younger cohort, whereas the opposite was true for ischemic stroke. The risk of AMI was significantly increased in DS individuals born in 1975–2000 (HR 6.95, 95% CI 2.16–22.36), but no increased risk was observed for those born in 1946–1974.

Discussion

In this large population-based cohort study, we found an increased risk for ischemic and hemorrhagic stroke in individuals with DS. The overall risk of AMI was similar in DS and non-DS individuals but higher in younger DS individuals. In DS, both selected atherosclerotic and cardioembolic risk factors were associated with an increased risk of ischemic but not hemorrhagic stroke. Both DS and non-DS individuals with selected cardiovascular risk factors were, however, at increased risk of AMI.

In our cohort, the risks of ischemic and hemorrhagic stroke were about four times higher in

Table 3. *Risk of stroke and AMI in individuals with and without cardiovascular risk factors.*

	Ischemic stroke		Hemorrhagic stroke		AMI	
	N cases	aHR (95% CI)	*N* cases	aHR (95% CI)	*N* cases	aHR (95% CI)
Embolic risk factors[a]						
Non-DS without embolic risk factors	1849	1.00 (ref)	1237	1.00 (ref)	2614	1.00 (ref)
Non-DS with embolic risk factors	479	4.33 (3.84–4.89)	117	1.85 (1.47–2.33)	567	3.04 (2.72–3.39)
DS without embolic risk factors	90	4.24 (3.27–5.49)	59	5.53 (3.99–7.68)	23	0.69 (0.41–1.15)
DS with risk embolic factors	31	10.35 (6.69–16.01)	12	4.43 (2.36–8.32)	9	3.23 (1.57–6.63)
Heart malformations						
Non-DS without heart malformations	2226	1.00 (ref)	1339	1.00 (ref)	3158	1.00 (ref)
Non-DS with heart malformations	102	15.72 (12.23–20.21)	15	2.69 (1.50–4.82)	23	2.13 (1.34–3.40)
DS without heart malformations	92	3.85 (2.97–4.98)	59	5.38 (3.88–7.47)	25	0.70 (0.43–1.13)
DS with heart malformations	29	11.17 (7.19–17.34)	12	4.58 (2.43–8.62)	7	2.49 (1.09–5.70)
Arrhythmias						
Non-DS without arrhythmias	1937	1.00 ref	1248	1.00 ref	2629	1.00 ref
Non-DS with arrhythmias	391	3.45 (3.02–3.94)	106	1.78 (1.39–2.27)[b]	552	3.09 (2.76–3.46)
DS without arrhythmias	116	4.78 (3.81–6.00)	70	5.20 (3.87–6.99)[b]	30	0.88 (0.57–1.36)
DS with arrhythmias	5	7.95 (2.33–27.13)	<5		<5	
Atherosclerotic risk factors[c]						
Non-DS without atherosclerotic risk factors	1741	1.00 (ref)	1160	1.00 (ref)	2331	1.00 (ref)
Non-DS with atherosclerotic risk factors	587	3.85 (3.44–4.31)	194	2.15 (1.77–2.61)[b]	850	3.91 (3.56–4.30)
DS without atherosclerotic risk factors	103	4.60 (3.61–5.86)	68	5.41 (4.00–7.31)[b]	26	0.85 (0.53–1.37)
DS with atherosclerotic risk factors	18	12.67 (7.04–22.78)	<5		6	3.30 (1.33–8.17)

(*Continued*)

Table 3. *(Continued)*

	Ischemic stroke *N* cases	aHR (95% CI)	Hemorrhagic stroke *N* cases	aHR (95% CI)	AMI *N* cases	aHR (95% CI)
Diabetes mellitus						
Non-DS without diabetes mellitus	1832	1.00 (ref)	1166	1.00 (ref)	2356	1.00 (ref)
Non-DS with diabetes mellitus	496	3.10 (2.75–3.49)	188	2.12 (1.74–2.58)[b]	825	3.89 (3.54–4.28)
DS without diabetes mellitus	103	4.43 (3.48–5.64)	68	5.40 (4.00–7.29)[b]	26	0.85 (0.53–1.36)
DS with diabetes mellitus	18	12.11 (6.74–21.78)	<5		6	3.29 (1.33–8.14)
Any cardiovascular risk factor[d]						
Non-DS without cardiovascular risk factors	1395	1.00 (ref)	1076	1.00 (ref)	1952	1.00 (ref)
Non-DS with cardiovascular risk factors	933	4.76 (4.30–5.25)	278	2.05 (1.73–2.42)	1229	3.98 (3.65–4.33)
DS without cardiovascular risk factors	73	4.28 (3.21–5.71)	56	5.80 (4.13–8.15)	18	0.65 (0.36–1.19)
DS with cardiovascular risk factors	48	12.45 (8.72–17.77)	15	4.66 (2.65–8.20)	14	3.54 (1.96–6.36)

Note: Effect modification analyses comparing risk of stroke and AMI in individuals with and without cardiovascular risk factors. Results show HRs for outcomes in different groups compared to non-DS individuals without risk factors. All analyses are adjusted for birth county, parental age and educational level, and sex.

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; DS, Down syndrome; HR, hazard ratio.

[a]Presence of heart malformations or arrhythmias. For details of included ICD codes, please refer to Tables S2 and S3.

[b]Does not fulfill the proportional hazard assumption and should be interpreted as the average HR over the whole study period.

[c]Presence of diabetes, cerebral atherosclerosis, occlusion, or stenosis of precerebral arteries. For details of included ICD codes, please refer to Tables S2 and S3.

[d]Presence of heart malformations, arrhythmias, diabetes, cerebral atherosclerosis, or occlusion or stenosis of precerebral arteries.

DS compared to the general population. In line with this, a recent large meta-analysis reported an increased risk for cerebrovascular disease in DS compared to the general population [17]. The same study observed sex differences within the DS population, with a higher risk of cerebrovascular disease in women [17], a finding that could not be replicated in our data. Moreover, in an Australian cohort of 4082 DS individuals, an increased risk of cerebrovascular events was observed [18]. Interestingly, the association with ischemic stroke was substantially attenuated after adjustment for cardioembolic, but not atherosclerotic, risk factors, suggesting that the risk of ischemic stroke was mainly explained by stroke of cardioembolic etiology [18]. Our results indicate that the increased risk of ischemic stroke in DS was mainly attributed to the presence of congenital heart disease or diabetes mellitus. However, despite an increased presence of diabetes in DS, we did not observe an increased overall risk of AMI, possibly suggesting a mechanism separate from atherosclerosis. We therefore speculate, in line with the findings from the Australian study [18], that ischemic stroke in DS is mainly of non-atherosclerotic etiology. This view is supported by previous data showing that DS individuals are protected from atherosclerosis and traditional vascular risk factors are not correlated to the presence of atherosclerosis to the same extent as in non-DS populations [14–16].

The increased risk of hemorrhagic stroke could not be explained by the risk factors included in our analyses. The role of non-included variables, such as hypertension, is thus unclear. However, previous studies suggest that the distribution of traditional vascular risk factors differs between DS and the general population, with a higher prevalence of obesity, sedentary lifestyle, and dyslipidemia, but a remarkably low prevalence of hypertension in DS [7, 8, 13]. Possibly, the increased risk could be related to Alzheimer's disease and amyloid pathology [25]. Comorbidities contributing to the increased risk of hemorrhagic stroke needs to be further investigated in cohorts with reliable measures of a wide spectrum of variables.

It should be noted that the median age at the end of follow-up in our study was around 40 years of age, and the prevalence of stroke in the general population is low in this age span [26]. Thus, our findings might reflect a general premature aging process in DS. Considering this, screening for DS-specific risk factors for stroke, such as congenital heart disease and diabetes, could be motivated from an earlier age in DS. International guidelines recommend diabetes screening in DS individuals starting at age 30 and for individuals with comorbid obesity as early as 21 years [12]. This seems reasonable to reduce diabetic complications, but based on our results, possibly also to reduce the risk of ischemic stroke. However, the specific risk factor profiles predicting stroke in DS needs to be further explored and defined.

We found similar overall risks of AMI among non-DS and DS individuals, a finding in line with the results from a cohort of 6078 hospitalized DS individuals from the United States [27]. Some studies have observed a lower risk of ischemic heart disease in DS compared to the general population, at least in individuals over 50 years of age [8, 18, 28], but an increased risk has also been reported [17]. In support of a possible age-dependent risk, we observed an increased risk of AMI <40 years of age in DS. In our study, the selected embolic as well as atherosclerotic risk factors increased the risk of AMI in both DS and non-DS individuals. The main risk factor categorized as atherosclerotic in our analyses was diabetes mellitus. This categorization was based on diabetes mellitus being a proxy variable for atherosclerotic disease in the general population. We found that diabetes was more prevalent in DS compared to the general population, which is in line with the observations from large population-based studies in the United Kingdom [8, 28]. However, despite the increased presence of diabetes, we did not observe an increased overall risk of AMI in DS. Considering this and the increased risk of AMI in younger but not older individuals with DS, our findings suggest that ischemic heart disease in DS may primarily arise from nonatherosclerotic causes, such as structural heart diseases. Another observation in our cohort was a low chance of having a coronary heart intervention among DS individuals, despite a similar risk of AMI as in the general population. This could be due to a higher prevalence of nonatherosclerotic etiologies in DS ischemic heart disease. However, there are alternative explanations, for instance, comorbidities and general health conditions in DS possibly preventing surgical procedures, thus the reasons underlying this observation should be further explored.

The main strength of the present study is its large cohort size and population-based design, which were made possible by national Swedish registers

and the use of the personal identification number. The validity of the registers is generally high and, especially for the specific outcomes of the present study, that is, stroke and AMI [20]. Although the study's large cohort and use of national Swedish registers support strong validity, some limitations should be noted. Primary care diagnoses like diabetes and atrial fibrillation may appear more often in the NPR for individuals with DS due to more frequent follow-ups in specialized clinics. Moreover, the lack of primary care data prevented us from including additional cardiovascular risk factors such as hypertension, hyperlipidemia, obesity, and smoking in the analyses of the present study. For DS diagnoses, specificity may be lower for individuals born before routine karyotyping, though we minimized misclassification by including only those with two or more DS diagnoses. Finally, the median age at end of follow-up was around 40 years suggesting that the observed cardiovascular risks in DS reflect an early onset but may not fully capture the lifetime risk.

In this large population-based cohort study, we found an increased risk of stroke in DS and an overall risk of AMI that was similar to the general population but increased in individuals younger than 40 years of age. These findings contradict the view that DS individuals are spared from cardiovascular outcomes due to the absence of atherosclerosis. Instead, our results indicate a different spectrum of cardiovascular risk factors in DS, which might have implications for screening measures as well as primary and secondary prevention strategies. These findings should inform future studies that aim to further investigate the pathophysiological mechanisms of cardiovascular diseases in DS, as well as healthcare systems developing guidelines fitted for the unique needs of the DS population.

Author contributions

Annie Pedersen: Writing — original draft; methodology; conceptualization; investigation. **Anna Skarin Nordenvall**: Conceptualization; writing — original draft; methodology; writing — review and editing; formal analysis; investigation. **Giorgio Tettamanti**: Writing — review and editing; methodology; supervision; investigation. **Ann Nordgren**: Conceptualization; funding acquisition; writing — review and editing; methodology; project administration; supervision; resources; investigation.

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Conflict of interest statement

The authors declare no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. ICD codes used to identify exposed individuals, i.e. Down syndrome.

Table S2. ICD codes used to identify cardiovascular outcomes.

Table S3. ICD codes used to identify cardiovascular risk factors.

Table S4. Results from adjusted Cox regression models showing Hazard ratios for outcomes in DS men and women as compared to non-DS.

Table S5. Results from adjusted Cox regression models showing Hazard ratios for outcomes in DS individuals as compared to non-DS in the full cohort, and stratified by year of birth. ■

