

Increased androgen-related comorbidity in adolescents and adults born with hypospadias: A population-based study

Lottie Phillips¹  | Cecilia Lundholm² | Ulrik Kvist³ | Catarina Almqvist^{2,4} |
Agneta Nordenskjöld^{1,5} | Anna Skarin Nordenvall^{2,6} 

¹Department of Women's and Children's Health, and Center of Molecular Medicine, Karolinska Institutet, Stockholm, Sweden

²Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

³Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden

⁴Pediatric Allergy and Pulmonology Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

⁵Department of Pediatric Surgery, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

⁶Department of Radiology, Karolinska University Hospital, Stockholm, Sweden

Correspondence

Dr Lottie Phillips, Department of Women's and Children's Health, Karolinska Institutet, J10:20 Bioclinicum, Akademiska stråket 1, 171 64 Solna, Sweden.
Email: lottie.phillips@ki.se

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Abstract

Background: Hypospadias is a common congenital malformation often related to the effect of androgens in utero. While hypogonadism is associated with many potential health risks including metabolic and cardiovascular disease, the risk of clinical hypogonadism and comorbidities in men with hypospadias later in life has not been studied.

Objectives: Investigate the risk of hypogonadism and somatic comorbidities in adolescents and men born with hypospadias.

Materials and methods: We conducted a population-based cohort study using Swedish registers. Associations between hypospadias and hypogonadism, delayed puberty, metabolic, and cardiovascular disease respectively were estimated using Cox proportional hazards regression. Body measurements from military conscription were analysed in a subpopulation as indicators of growth and cardiometabolic risk. We used sibling comparison analyses to control for familial confounding.

Results: Using register data, a total of 2,165,255 men including 9,714 men born with hypospadias were followed from the age of 10 to a maximum of 60 years. We found an association between hypospadias and hypogonadism (Hazard ratio (HR) 3.27, 95% confidence interval (CI) 2.33–4.59) which was more pronounced in proximal hypospadias. Men with hypospadias had shorter average height than their brothers and the general population. We further found an increased risk of delayed puberty (HR 1.49, 95% CI 1.08–2.07), diabetes mellitus type 2 (HR 1.57, 95% CI 1.18–2.09) and cardiovascular disease (HR 1.47, 95% CI 1.27–1.71).

Discussion: We found an increased risk of hypogonadism, metabolic and cardiovascular disease in men born with hypospadias, increasing with severity of phenotype, as well as impacted growth. These results indicate disruptions in androgen function past childhood, although some of the associations may be due to other underlying aetiologies.

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Conclusion: Hypospadias is associated with an increased risk of androgen-related comorbidity in adolescence and adulthood. We suggest that this can be considered clinically, while further research is needed, especially in older populations.

KEYWORDS

cardiovascular diseases, cohort design, diabetes mellitus, growth, hypogonadism, hypospadias

1 | INTRODUCTION

Hypospadias is a common congenital malformation with a prevalence in Sweden of one in 125 boys, defined by the ectopic placement of the urethral opening along the ventral side of the penis, varying across a spectrum from distal to proximal.¹ Hypospadias has a complex aetiology and can, depending on the underlying biological mechanisms, be associated with many other malformations, especially cryptorchidism.² As testosterone and dihydrotestosterone (DHT) influence the development of male external genitalia, the aetiology of hypospadias is thought to often be due to a disruption in foetal androgens, in some cases caused by genetic mutations. Important environmental risk factors relate to intrauterine growth restriction: low birth weight, placental insufficiency, and maternal preeclampsia. It has been hypothesised that impaired placental function causes diminished androgen effects through lowered production of human chorionic gonadotropin (hCG).³

A small number of men born with hypospadias are known to have continued hypoandrogenism throughout life due to specific genetic causes, and more can be hypothesised to be affected in adolescence or adulthood. Studies by Asklund et al. and Kumar et al. have shown that men with hypospadias overall have lower testosterone levels and higher luteinizing hormone (LH) levels compared to controls, indicating decreased testicular production of testosterone.^{4,5}

Dysfunction anywhere on the hypothalamic–pituitary–gonadal axis in boys or men can cause the clinical syndrome hypogonadism. Presentation depends on the age of onset but can include delayed puberty, decreased sperm production, and negative effects on mood and cognition.⁶ Hypogonadism is known to be strongly associated with obesity and type 2 diabetes, with underlying bidirectional causal associations.⁷ Several studies in recent years have also found an association between low testosterone and cardiovascular disease, although the nature of the association remains largely uncertain.^{8,9} While testosterone replacement therapy has many positive effects on symptoms and body constitution, the risks and benefits with regards to cardiovascular disease require further investigation.^{10,11}

The risk of clinical hypogonadism and potential somatic comorbidities, including metabolic and cardiovascular disease, has not been studied in men with hypospadias. Hypogonadism is a treatable condition which affects development, health, and well-being, and may be easily missed clinically given the non-specific symptoms, while cardiovascular and metabolic disorders are major global causes of morbidity and mortality. This study therefore aimed to investigate the risk of clinical hypogonadism and associated somatic comorbidities in adolescents

and men born with hypospadias using a nationwide cohort design. We hypothesised that the risk of both hypogonadism and related somatic disorders would be increased. In order to further explore potential biological mechanisms, we also aimed to investigate how associated malformations and intrauterine growth restriction impact the risk of androgen-related comorbidity, as well as the role of shared genetic and environmental factors using sibling comparison analyses.

2 | MATERIALS AND METHODS

This study is reported in accordance with the STROBE guidelines for observational studies. Ethical permission was granted by the Swedish Ethical Review Authority.

National Swedish registers were used to collect data. Demographic data, including date of birth, migration, and death, was taken from the Total Population Registry maintained by Statistics Sweden from 1968 and the National Swedish Census of 1960 for those who turned 10 before 1968.¹² The Swedish Military Conscription Registry (SMCR) contains data from measurements and tests performed during the process of military conscription around the age of 19. The National Board and Health and Welfare maintain the National Patient Registry (NPR), registering in-patient care from 1964 and out-patient specialist care from 2001, and the Medical Birth Registry (MBR) which registers pre- and perinatal covariates relating to mother and child since 1973.^{13,14} Data are not specifically reported by doctors to these registers but are instead taken from the data and diagnoses registered in medical records, making the coverage for in-patient care close to 100% in recent decades.¹³ Data across registers were linked using a personal identity number which is given to all Swedish residents and is unique and specific to the individual.¹⁵ All data were pseudonymised by Statistics Sweden prior to use.

We used a cohort study design. The study population consisted of boys and men born 1954–2003 who at an age of 10 lived in any Swedish county with full coverage in the NPR (Figure 1, further detail in Appendix p1).

2.1 | Exposure and outcomes

All diagnoses were classified using the International Classification of Diseases (ICD-7-ICD-10) (Appendix p4–6). The study exposure was hypospadias. Phenotype specific codes were used in ICD-8 and ICD-10

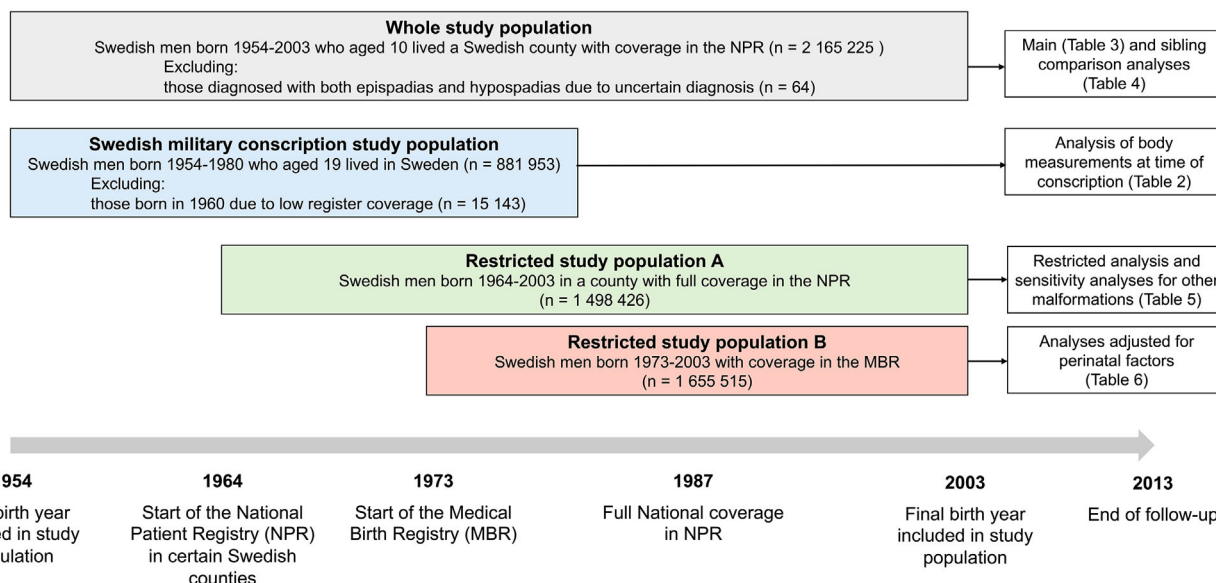


FIGURE 1 Study populations and data sources. Birth years of the study populations used in different analyses are plotted against a time axis, with the corresponding results tables listed to the right. Men born after 1980 were excluded from the military conscription study population (blue) as the national rate of conscription gradually dropped after that year, while men born 1960 were excluded due to very low registry coverage (circa 15%). For the years included 85.9%–99.6% of men in the study population were registered in the SMCR with a total of 95.7%. Only men who lived in Sweden the year they turned 19 and were therefore eligible for conscription were included. Restricted population A (green) was used to assess whether those diagnosed with hypospadias up to 10 years of age are representative of the whole patient cohort, as well as for sensitivity analyses for cryptorchidism and for extragenital malformations or chromosome aberrations (to assess the impact of comorbidity), as many malformations are diagnosed and treated in infancy or early childhood

to define distal and proximal hypospadias, respectively. Any individual diagnosed at least once in either the NPR or the MBR was defined as having hypospadias. As measures of growth and early indicators of cardiometabolic risk, data on height, weight, systolic and diastolic blood pressure were taken from the SMCR. Body mass index (BMI) (kg/m^2) was calculated using height and weight. Disease outcomes were identified using the NPR and included hypogonadism, delayed puberty, diabetes mellitus, obesity, and cardiovascular disease.

2.2 | Covariates

Confounding pathways for the associations between hypospadias and hypogonadism, metabolic, and cardiovascular disease respectively were identified using directed acyclic graphs (DAGs) based on previous literature and biological plausibility (Appendix p1-3). Mothers' place of birth was used as a proxy for ethnicity. The multi-generation register maintained by Statistics Sweden was used to link index persons to their biological mothers. The perinatal covariates birth weight, birth length, gestational age, and maternal preeclampsia were identified using the MBR. Diagnosis of any extragenital malformations and chromosome aberrations (not including sex chromosomes) was identified using both the NPR and the MBR, while cryptorchidism was defined by both diagnosis and surgical treatment from the NPR (Appendix p6). Treatment with testosterone was assessed using the Prescribed Drug Register which registers all drug prescriptions in Sweden that are dispensed at pharmacies, including primary care, since 2005. Treatment

data were used to improve hypogonadism classification accuracy and for descriptive statistics. Certain covariates were categorised using common categorizations prior to analysis (Table 1).

2.3 | Statistical analysis

Multiple linear regression was used to estimate the associations between hypospadias and the continuous outcome variables from the SMCR. Biologically implausible values for each outcome variable were excluded prior to analysis. Residuals were plotted to check for linearity and homoscedasticity. Robust standard errors were used to account for minor violations of the assumption homoscedasticity. The regression coefficients were adjusted for birth weight, gestational age, birth year, and mothers' country of birth as potential confounders.

Cox proportional hazards regression analysis was used to estimate the associations between hypospadias and diagnoses outcomes from the NPR. Schoenfeld's residuals were used to test for proportional hazards. The Cox model was stratified by covariates where the test indicated non-proportional hazards. For the outcome hypogonadism, Kaplan–Meier survival analysis was used to estimate the disease-free survival proportions across the follow-up period in men with hypospadias as well as the general male population. The main analyses were conducted (crude and adjusted) in the full population (born from 1954). Further restricted populations were used for specific analyses including sensitivity analyses (Figure 1). Sibling comparison analyses were performed on all full sibling pairs (brothers) in the full cohort, after

TABLE 1 Characteristics of the whole study population. Prevalence of outcomes and covariates amongst exposed and unexposed. Note that the number of observed outcomes in men with hypospadias compared to controls is impacted by the generally younger age of men with hypospadias in the study population. All numbers (N) less than 5 are not included in the table and are instead marked as NA = not applicable

	Any hypospadias	Distal hypospadias	Proximal hypospadias	No hypospadias	Total
N (%)	9,714 (0.45)	6,142 (0.28)	689 (0.03)	2,155,511 (99.55)	2,165,225
Birth year					
1954–1963	114 (1.17)	52 (0.85)	6 (0.87)	124,758 (5.79)	124,872 (5.77)
1964–1972	872 (8.98)	501 (8.16)	53 (7.69)	383,966 (17.81)	384,838 (17.77)
1973–1982	2,230 (22.96)	1,843 (30.01)	77 (11.18)	496,334 (23.03)	498,564 (23.03)
1983–1992	2,729 (28.09)	1,024 (16.67)	145 (21.04)	579,424 (26.88)	582,153 (26.89)
1993–2003	3,769 (38.80)	2,722 (44.32)	408 (59.22)	571,029 (26.49)	574,798 (26.55)
Mother's country of birth					
Nordic Country (including Sweden)	8,277 (85.21)	5,263 (85.69)	556 (80.70)	1,905,260 (88.39)	1,913,537 (89.37)
Greater Europe	660 (6.79)	412 (6.71)	41 (5.95)	107,344 (4.98)	108,004 (5.04)
Africa	134 (1.38)	85 (1.38)	21 (3.05)	21,369 (0.99)	21,503 (1.00)
Asia	495 (5.10)	307 (5.00)	56 (8.13)	74,247 (3.44)	74,742 (3.49)
Other	67 (0.69)	34 (0.55)	7 (1.02)	23,317 (1.08)	23,384 (1.09)
Missing	81 (0.83)	41 (0.67)	8 (1.16)	23,974 (1.11)	24,055 (1.11)
Hypogonadism	41 (0.42)	19 (0.31)	16 (2.32)	3,360 (0.16)	3,401 (0.16)
Primary hypogonadism	30 (0.31)	11 (0.18)	15 (2.18)	2,049 (0.10)	2,079 (0.10)
Proportion primary hypogonadism (%)	73	58	94	61	61
Secondary hypogonadism	15 (0.15)	9 (0.15)	NA	1,659 (0.08)	1,674 (0.08)
Testosterone treatment ^a	72 (0.74)	36 (0.59)	23 (3.34)	7,662 (0.36)	7,734 (0.36)
Delayed puberty	51 (0.53)	28 (0.46)	13 (1.89)	5,755 (0.27)	5,806 (0.27)
Any metabolic disease (type 2 DM or obesity)	191 (1.97)	115 (1.87)	24 (3.48)	41,083 (1.91)	41,274 (1.91)
Diabetes mellitus (any)	124 (1.28)	73 (1.19)	10 (1.45)	29,099 (1.35)	29,223 (1.35)
Diabetes mellitus type 2	48 (0.49)	26 (0.42)	5 (0.73)	12,923 (0.60)	12,971 (0.60)
Obesity	155 (1.60)	92 (1.50)	22 (3.19)	31,099 (1.44)	31,254 (1.44)
Any cardiovascular disease	192 (1.98)	121 (1.97)	8 (1.16)	51,733 (2.40)	51,925 (2.40)
Myocardial infarction or stroke	22 (0.23)	11 (0.18)	NA	7,231 (0.34)	7,253 (0.33)
Hypertension	103 (1.06)	64 (1.04)	NA	30,785 (1.43)	30,888 (1.43)
Coronary heart disease	20 (0.21)	12 (0.20)	NA	7,546 (0.35)	7,566 (0.35)
Cerebrovascular disease including cerebral infarction	19 (0.20)	12 (0.20)	NA	5,608 (0.26)	5,627 (0.26)
Congestive heart failure	26 (0.27)	10 (0.16)	NA	4,387 (0.20)	4,413 (0.20)
Born from 1973 onwards					
Extragenital malformation or chromosome aberration	1,717 (19.67)	995 (17.80)	246 (39.05)	122,696 (7.45)	124,413 (7.52)
Cryptorchidism	376 (4.31)	169 (3.02)	108 (17.14)	19,913 (1.21)	20,289 (1.23)
Gestational age at delivery (weeks)					
≤31	185 (2.12)	91 (1.63)	47 (7.46)	9,619 (0.58)	9,804 (0.59)
32–36	847 (9.70)	487 (8.71)	104 (16.51)	79,343 (4.82)	80,190 (4.84)
37–42	7,098 (81.32)	4,664 (83.45)	415 (65.87)	1,407,700 (85.48)	1,414,798 (85.46)
≥43	148 (1.70)	115 (2.06)	5 (0.79)	19,374 (1.18)	19,522 (1.18)
Missing	450 (5.16)	232 (4.15)	59 (9.37)	130,751 (7.94)	131,201 (7.93)

(Continues)

TABLE 1 (Continued)

	Any hypospadias	Distal hypospadias	Proximal hypospadias	No hypospadias	Total
Birth weight (g)					
<2500	956 (10.95)	507 (9.07)	173 (27.46)	55,666 (3.38)	56,622 (3.42)
2500–4500	7,050 (80.77)	4,659 (83.36)	379 (60.16)	1,395,492 (84.7)	1,402,542 (84.72)
>4500	265 (3.04)	187 (3.35)	14 (2.22)	64,260 (3.90)	64,525 (3.90)
Missing	457 (5.24)	236 (4.22)	64 (10.16)	131,369 (7.98)	131,826 (7.96)
Maternal preeclampsia	362 (4.15)	206 (3.69)	75 (11.90)	34,529 (2.10)	34,891 (2.11)

^aPrescription of testosterone in any form Anatomical Therapeutic Chemical (ATC) code G03B between 2005 and 2013.

exclusion of multiple births, in order to adjust for observed and unobserved shared genetic and environmental familial factors. Fixed effects' linear regression was used for the sibling comparison analyses on military conscription data, while stratified Cox regression was used for diagnoses outcomes.

All statistical analyses are performed using STATA 17.0.

3 | RESULTS

A total of 2,165,225 men were included in the study population (Figure 1). A total of 9,714 men had been diagnosed with hypospadias, including 6,142 with distal hypospadias and 689 with proximal hypospadias (Table 1). Of men with hypospadias, 41 (0.42%) had been diagnosed with hypogonadism as compared to 3,360 (0.16%) in the general male population. Kaplan–Meier survival analysis showed that men with hypospadias are diagnosed with hypogonadism at an earlier age and to a greater extent than men without hypospadias, especially those with proximal hypospadias (Figure 2).

A total of 881,953 men were included in the analysis of conscription data. Men with hypospadias were generally slightly shorter than the general male population (mean 178.63 cm and 179.44 cm, respectively), while men with proximal hypospadias had a mean height almost 5 cm lower than men without hypospadias (Table 2). Linear regression analysis showed a significant association with decreased height for all phenotypes which was no longer present after adjusting for birth weight. In sibling comparison analysis, we found that men with hypospadias overall were shorter than their unexposed brothers and men with proximal hypospadias were shorter even after adjusting for birth weight and gestational week. Men born with hypospadias had largely equivalent BMI and blood pressure at the age of conscription, with regression coefficients close to 0. We found a small association with increased diastolic blood pressure in adjusted analysis for men with proximal hypospadias (coeff. 2.81, 95% CI 0.06, 5.55), while the estimate for systolic blood pressure was coeff. = 2.28 (95% CI –0.70, 5.25) (Appendix p7).

When investigating diagnoses outcomes from the NPR, the cohort was followed from the age of 10 until a maximum age of 60, with a total follow-up time of almost 43 million person-years. Men without hypospadias had a mean follow-up time of 19.8 years, while men

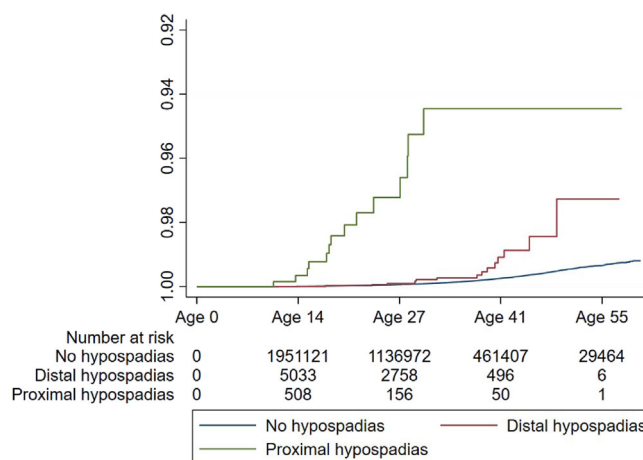


FIGURE 2 Kaplan–Meier survival estimates for the association between hypospadias and hypogonadism by phenotype. Kaplan–Meier survival estimates for distal (red) and proximal (green) hypospadias, respectively, as compared to no hypospadias (blue). The whole study population was followed from the age of 10 until the outcome of interest, migration, death, or the end of the study period (20131231). The inverted y-axis spans from a disease-free survival proportion of 1 to 0.92

with hypospadias had a mean of 15.6 years. Cox proportional hazards regression showed an increased risk of hypogonadism in men with hypospadias (HR 3.27, 95% CI 2.33–4.59) (Table 3). When analysing primary and secondary hypogonadism separately, we found that both were associated with hypospadias (HR 3.86, 95% CI 2.51–5.94 as compared to HR 2.58, 95% CI 1.38–4.81). The proportional hazards assumption was not fulfilled for primary hypogonadism as the ratio increased with age. Therefore, the HR should be interpreted as a weighted average over the follow-up time (age).

We further found an increased risk of delayed puberty (HR 1.49, 95% CI 1.08–2.07), and type 2 diabetes (HR 1.57, 95% CI 1.18–2.09). We found a weaker association between diabetes mellitus overall and hypospadias, and no clear association between any hypospadias and overall metabolic disease or obesity. The associations were stronger in men with proximal hypospadias, who also had an increased risk of obesity. Hypospadias was associated with an increased risk of overall cardiovascular disease (HR 1.47, 95% CI 1.27–1.71) as well as specifically

TABLE 2 Body measurements as indicators of growth and cardiometabolic risk at time of military conscription Data from the Swedish Military Conscription register at time of conscription (ca. 19 years of age) from a total of 881,953 men born 1954–1980 (1960 excluded) of whom 2,733 men had hypospadias including 2,048 men with distal hypospadias and 123 men with proximal hypospadias. Biologically implausible values and missing data (% presented in table) were excluded from analysis

	Any hypospadias	Distal hypospadias	Proximal hypospadias	No hypospadias
Height (cm), Mean (SD)	178.63 (6.99)	178.88 (6.77)	174.62 (9.01)	179.44 (6.59)
Missing (%)	11.9	11.3	19.5	8.2
Weight (kg), Mean (SD)	70.67 (11.68)	71.02 (11.76)	66.78 (10.96)	70.92 (10.95)
Missing (%)	11.9	11.3	19.5	8.2
BMI (kg/m ²) ^a , Mean (SD)	22.12 (3.22)	22.16 (3.27)	21.85 (2.97)	22.00 (3.03)
Systolic blood pressure (mmHg), Mean (SD)	128.85 (10.67)	128.76 (10.60)	129.78 (11.59)	128.60 (10.85)
Missing (%)	14.5	14.1	20.3	10.2
Diastolic blood pressure (mmHg), Mean (SD)	66.69 (9.84)	66.53 (9.76)	67.49 (10.39)	66.39 (9.88)
Missing (%)	14.5	14.1	20.3	10.3

^aCalculated using registered height and weight.

TABLE 3 Main crude and adjusted associations between hypospadias and androgen-related comorbidity in the whole study population born 1954–2003. Timescale is attained age. The study population was followed from the age of 10 until the outcome of interest, migration, death, or the end of the study period (20131231). Adjusted HR is adjusted for maternal ethnicity and year of birth. Analyses with N less than 5 were not performed and instead marked with NA = not applicable

	Crude HR (95% CI)			Adjusted HR (95% CI)		
	Any hypospadias	Distal hypospadias	Proximal hypospadias	Any hypospadias	Distal hypospadias	Proximal hypospadias
Hypogonadism	4.09 (2.93–5.71)	2.73 (1.64–4.54)	35.4 (21.0–59.9) ^a	3.27 (2.33–4.59)	2.23 (1.34–3.71)	27.4 (15.9–47.3) ^a
Delayed puberty ^b	1.69 (1.23–2.31)	1.67 (1.11–2.51)	6.75 (3.51–12.99)	1.49 (1.08–2.07)	1.68 (1.11–2.56)	4.39 (2.19–8.78)
Any metabolic disease (type 2 DM or obesity)	1.43 (1.22–1.68)	1.32 (1.07–1.63)	3.16 (1.99–5.01)	1.16 (0.98–1.36)	1.08 (0.88–1.34)	2.03 (1.26–3.26)
Diabetes mellitus (any)	1.30 (1.06–1.60)	1.17 (0.89–1.54)	1.89 (0.90–3.97)	1.24 (1.01–1.52)	1.14 (0.86–1.50)	1.51 (0.68–3.35)
Diabetes mellitus type 2 ^c	1.62 (1.22–2.15)	1.40 (0.96–2.06)	3.54 (1.47–8.50)	1.57 (1.18–2.09)	1.39 (0.95–2.05)	2.77 (1.04–7.40)
Obesity	1.35 (1.13–1.63)	1.21 (0.95–1.55)	3.40 (2.08–5.55)	1.07 (0.89–1.28)	0.97 (0.76–1.24)	2.05 (1.24–3.41)
Any cardiovascular disease	1.61 (1.39–1.87)	1.68 (1.39–2.02)	NA	1.47 (1.27–1.71)	1.53 (1.27–1.84)	NA
Cerebral or myocardial infarction	1.65 (1.07–2.53)	1.31 (0.70–2.43)	NA	1.60 (1.04–2.46)	1.27 (0.68–2.37)	NA
Hypertension	1.64 (1.34–2.00)	1.68 (1.30–2.16)	NA	1.48 (1.21–1.81)	1.48 (1.15–1.91)	NA
Coronary heart disease	1.60 (1.03–2.48)	1.63 (0.93–2.87)	NA	1.65 (1.06–2.56)	1.72 (0.98–3.04)	NA
Cerebrovascular disease incl. cerebral infarction	1.43 (0.88–2.34)	1.31 (0.68–2.52)	NA	1.34 (0.82–2.18)	1.21 (0.63–2.33)	NA
Congestive heart failure	2.31 (1.47–3.62)	1.78 (0.92–3.42)	NA	2.05 (1.29–3.26)	1.68 (0.87–3.23)	NA

^aAnalysis for proximal hypospadias had non-proportional hazards due to the early and dramatic increase in risk for men with proximal hypospadias. The exact estimated HR should be interpreted with caution, and focus put on the confidence interval.

^bDelayed puberty is analysed from the start of ICD-9 (1987), between the ages of 14 and 20.

^cDiabetes mellitus type 2 is analysed from the age of 10 or the start of ICD-10 (1997), whichever occurred last.

cerebral or myocardial infarction, hypertension and coronary heart disease. The largest association was with congestive heart failure (HR 2.05, 95% CI 1.29–3.26), while we could not show a clear association with cerebrovascular disease alone (HR 1.34, 95% CI 0.82–2.18) (Table 3).

A total of 999,076 individuals were included in sibling analyses. The estimate for hypogonadism was reduced in distal hypospadias

but largely unchanged for any hypospadias, while the estimate for delayed puberty was unchanged for any hypospadias but increased in distal hypospadias. The estimates for diabetes were reduced. The estimates were similar for any cardiovascular disease and hypertension, and reduced for congestive heart failure (Table 4). Analysis restricted to 1964 showed similar results to the full cohort except for certain cardiovascular outcomes strongly related to age. Excluding men

TABLE 4 Sibling comparison analyses for the associations between hypospadias and androgen-related comorbidity in the whole study population born 1954–2003. Timescale is attained age. The study population was followed from the age of 10 until the outcome of interest, migration, death, or the end of the study period (20131231). The first analysis is adjusted for maternal ethnicity and year of birth. The sibling analysis includes full sibling pairs in the study population, stratified by sibling pair and adjusted for birth year and parity (i.e., first child of biological mother or not) as confounders which vary between siblings. All multiple births are excluded from the study population. Analyses with *N* less than 5 were not performed and instead marked with NA = not applicable

	Sibling comparison analysis HR (95% CI)		
	Any hypospadias	Distal hypospadias	Proximal hypospadias
Hypogonadism	2.93 (0.83–10.39)	1.01 (0.22–4.61)	NA
Delayed puberty ^a	1.44 (0.64–3.24)	2.68 (0.74–9.77)	NA
Diabetes mellitus (any)	0.95 (0.57–1.60)	0.75 (0.37–1.52)	NA
Diabetes mellitus type 2 ^b	0.98 (0.42–2.30)	1.15 (0.36–3.64)	NA
Any cardiovascular disease	1.62 (1.11–2.36)	1.42 (0.90–2.25)	NA
Hypertension	1.44 (0.84–2.47)	1.37 (0.70–2.68)	NA
Congestive heart failure	1.04 (0.33–3.26)	NA	NA

^aDelayed puberty is analysed from the start of ICD-9, between the ages of 14 and 20.

^bDiabetes mellitus type 2 is analysed from the age of 10 or the start of ICD-10 (1997), whichever occurred last.

with cryptorchidism in sensitivity analyses generally had no or little impact, although the estimates for hypogonadism and delayed puberty were partially reduced. Excluding men with extragenital malformations and chromosome aberrations (sex chromosome aberrations were not excluded) partially reduced effect estimates for cardiovascular disease (Table 5). Adjusting for perinatal factors primarily reduced the estimates for metabolic disease, although proximal hypospadias was still associated with metabolic disease and obesity after adjustment (Table 6).

4 | DISCUSSION

This nationwide Swedish study conducted using register data showed an increased risk of hypogonadism in adolescents and men born with hypospadias. We further found that adolescents with hypospadias have an increased risk of delayed puberty, reach a lower adult height than their male siblings and the general population but have largely equivalent BMI and blood pressure. We found associations between hypospadias and type 2 diabetes mellitus and overall cardiovascular disease, whereas obesity was only associated with proximal hypospadias. Associations were generally more pronounced in men with proximal hypospadias and could not be fully explained by perinatal covariates, associated malformations or familial factors shared by siblings.

Our findings are congruent with previous studies conducted on small populations of adult men born with hypospadias showing generally lower testosterone and higher LH compared to controls.^{4,5} Disruptions in androgen function have especially been shown in severe hypospadias or hypospadias associated with related comorbidities such as cryptorchidism, but less certainly in isolated, mild hypospadias.^{4,5,16} Hypogonadism later in life in men with hypospadias may in some cases result from genetic causes of impaired androgen

production or metabolism, or partial androgen insensitivity. In other cases, the testes may have developed abnormally. Our Kaplan–Meier survival analysis showed that men with proximal hypospadias diagnosed with hypogonadism after the age of 10 were diagnosed during adolescence or young adulthood, which may reflect the high demand on the androgen function during puberty and for fertility. Men with distal hypospadias were also diagnosed earlier in general than men without hypospadias, possibly indicating functional decline at an earlier age. Testicular dysgenesis has been theoretically linked to both hypospadias and cryptorchidism.¹⁷ The decrease in our effect estimates after exclusion of men with cryptorchidism indicates that the association is partly due to but cannot be fully explained by comorbidity with cryptorchidism. Though the increased risk of hypogonadism in men with a history of cryptorchidism or more severe forms of disorders of sex development is more established, this is the first study to show an association with hypospadias.^{6,18} In separate analyses, we found that both primary and secondary hypogonadism were significantly associated with hypospadias, although the association was somewhat stronger for primary hypogonadism. While almost all men with proximal hypospadias who had hypogonadism were specifically diagnosed with testicular hypofunction, equivalent proportions of primary and secondary hypogonadism were diagnosed in men with distal hypospadias in our study population. This is congruent with the results of Moriya et al. who in 43 adolescents with hypospadias only identified hypogonadotropic hypogonadism in distal hypospadias, indicating possible differences across phenotypes.¹⁹ As diagnosis data are from specialist care and international guidelines require hormone testing, it is unlikely that men identified as having hypogonadism in our study would have been incorrectly diagnosed. However, we do not have data on hormone profiles and therefore cannot verify correct diagnosis in this study. Testosterone treatment is the most sensitive measure of hypogonadism in our study as it includes primary care, with a roughly 10-fold higher prevalence in men with proximal hypospadias than controls.

TABLE 5 Associations between hypospadias and androgen-related morbidity in restricted study population A born 1964–2003 with sensitivity analyses for other malformations. Timescale is attained age. The study population was followed from the age of 10 until the outcome of interest, migration, death, or the end of the study period (2013/231). All analyses are adjusted for maternal ethnicity and year of birth and performed on restricted population A consisting of men in the whole study population born in a Swedish county with full registry coverage. In the analysis excluding other malformations, all extragenital malformations and somatic chromosome aberrations were excluded (Appendix [pc](#)). Analyses with N less than 5 were not performed and instead marked with NA = not applicable

	Adjusted HR (95% CI)			Excluding cryptorchidism HR (95% CI)			Excluding other malformations HR (95% CI)		
	Any hypospadias	Distal hypospadias	Proximal hypospadias	Any hypospadias	Distal hypospadias	Proximal hypospadias	Any hypospadias	Distal hypospadias	Proximal hypospadias
Hypogonadism	3.19 (2.12–4.82)	1.91 (0.99–3.68)	34.2 (18.9–62.0)	1.85 (1.05–3.27)	1.63 (0.77–3.42)	NA	2.65 (1.56–4.49)	1.69 (0.76–3.78)	33.8 (15.1–75.5)
Delayed puberty ^a	1.44 (1.03–2.01)	1.65 (1.08–2.54)	3.93 (1.87–8.26)	1.23 (0.85–1.78)	1.56 (0.99–2.45)	NA	1.16 (0.75–1.77)	1.54 (0.93–2.56)	NA
Any metabolic disease (type 2 DM or obesity)	1.05 (0.87–1.27)	0.97 (0.75–1.24)	2.18 (1.32–3.62)	1.05 (0.86–1.27)	0.99 (0.77–1.27)	2.18 (1.24–3.84)	1.05 (0.85–1.31)	0.97 (0.73–1.28)	1.58 (0.71–3.52)
Diabetes mellitus (any)	1.19 (0.92–1.54)	1.04 (0.74–1.48)	NA	1.17 (0.90–1.52)	1.05 (0.74–1.49)	NA	1.15 (0.86–1.55)	0.94 (0.62–1.41)	NA
Diabetes mellitus type 2 ^b	1.60 (1.08–2.37)	1.24 (0.72–2.15)	NA	1.43 (0.93–2.20)	1.21 (0.69–2.13)	NA	1.57 (1.00–2.47)	1.22 (0.66–2.28)	NA
Obesity	0.96 (0.77–1.18)	0.89 (0.67–1.18)	2.06 (1.19–3.54)	0.97 (0.78–1.21)	0.92 (0.70–1.22)	2.17 (1.20–3.91)	0.96 (0.76–1.23)	0.90 (0.66–1.23)	1.73 (0.78–3.85)
Any cardiovascular disease	1.53 (1.25–1.88)	1.55 (1.21–1.99)	NA	1.51 (1.22–1.86)	1.52 (1.18–1.96)	NA	1.20 (0.91–1.58)	1.32 (0.96–1.81)	NA
Cerebral or myocardial infarction	1.30 (0.62–2.73)	NA	NA	1.38 (0.66–2.90)	NA	NA	NA	NA	NA
Hypertension	1.54 (1.16–2.05)	1.57 (1.11–2.20)	NA	1.51 (1.12–2.03)	1.54 (1.08–2.19)	NA	1.27 (0.88–1.82)	1.33 (0.87–2.04)	NA
Coronary heart disease	1.23 (0.51–2.96)	NA	NA	1.32 (0.55–3.19)	NA	NA	NA	NA	NA
Cerebrovascular disease incl. cerebral infarction	1.12 (0.53–2.36)	NA	NA	1.19 (0.56–2.49)	NA	NA	1.17 (0.49–2.82)	NA	NA
Congestive heart failure	2.20 (1.18–4.10)	1.72 (0.71–4.14)	NA	2.12 (1.104.09)	1.81 (0.75–4.37)	NA	1.81 (0.75–4.35)	NA	NA

^a Delayed puberty is analysed from the start of ICD-9, between the ages of 14 and 20.

^b Diabetes mellitus type 2 is analysed from the age of 10 or the start of ICD-10 (1997), whichever occurred last.

TABLE 6 Associations between hypospadias and androgen-related comorbidity in restricted population B born 1973–2003 with adjustment for perinatal covariates. Timescale is attained age. The study population was followed from the age of 10 until the outcome of interest, migration, death, or the end of the study period (2013/231). Adjusted HR is adjusted for birth year, maternal ethnicity, gestational age, birth weight, and maternal preeclampsia. Analyses with N less than 5 were not performed and instead marked with NA = not applicable

	Crude HR (95% CI)			Adjusted HR (95% CI)		
	Any hypospadias	Distal hypospadias	Proximal hypospadias	Any hypospadias	Distal hypospadias	Proximal hypospadias
Hypogonadism	3.37 (2.29–4.96) ^a	1.61 (0.84–3.10)	48.3 (28.5–81.7)	3.13 (2.08–4.69)	1.69 (0.88–3.26)	38.4 (21.3–69.2)
Delayed puberty ^b	1.69 (1.23–2.31)	1.67 (1.11–2.51)	6.75 (3.51–12.99)	1.39 (1.00–1.95)	1.60 (1.04–2.45)	3.56 (1.69–7.49)
Any metabolic disease (type 2 DM or obesity)	1.20 (1.00–1.44)	1.03 (0.81–1.31)	3.19 (1.95–5.20)	1.05 (0.87–1.27)	0.99 (0.77–1.26)	1.99 (1.16–3.44)
Diabetes mellitus (any)	1.29 (1.01–1.63)	1.06 (0.77–1.46)	1.87 (0.78–4.50)	1.16 (0.90–1.49)	1.06 (0.77–1.48)	1.09 (0.35–3.37)
Diabetes mellitus type 2	1.68 (1.16–2.43)	1.13 (0.67–1.90)	NA	1.32 (0.86–2.00)	1.09 (0.63–1.88)	NA
Obesity	1.11 (0.91–1.36)	0.98 (0.75–1.27)	3.08 (1.82–5.20)	0.99 (0.80–1.22)	0.93 (0.71–1.22)	1.86 (1.03–3.37)
Any cardiovascular disease	1.43 (1.16–1.75)	1.35 (1.05–1.72)	NA	1.31 (1.06–1.62)	1.29 (1.00–1.66)	NA
Cerebral or myocardial infarction	1.16 (0.52–2.58)	NA	NA	1.12 (0.50–2.51)	NA	NA
Hypertension	1.24 (0.90–1.69)	1.13 (0.77–1.65)	NA	1.16 (0.84–1.61)	1.12 (0.76–1.64)	NA
Cerebrovascular disease incl. cerebral infarction	0.78 (0.33–1.87)	NA	NA	0.76 (0.32–1.83)	NA	NA
Congestive heart failure	2.50 (1.42–4.42)	1.74 (0.78–3.88)	NA	2.09 (1.12–3.90)	1.52 (0.63–3.65)	NA

^aSlight trend towards decreased HR over time, with very low hazard at the age of 10 amongst unexposed.

^bDelayed puberty is analysed from the start of ICD-9, between the ages of 14 and 20.

^cDiabetes mellitus type 2 is analysed from the age of 10 or the start of ICD-10 (1997), whichever occurred last.

Our results show that men with hypospadias have a larger risk of delayed puberty as well as lower adult height, but equivalent adolescent BMI. Arendt et al. also showed in a Danish cohort study that hypospadias was possibly associated with delayed pubertal development.²⁰ Delayed puberty has strong heritability and is often present in several members of a family.²¹ The results of the sibling analysis indicate that the increased risk of both delayed puberty and hypogonadism cannot be explained by shared familial factors. While there may be different underlying causes of delayed puberty amongst boys with hypospadias, the associations between delayed puberty and hypogonadism are likely in some way linked.²¹ The lack of an association between hypospadias and BMI in this study indicates that the increased risk of cardiovascular disease and type 2 diabetes may be independent of weight. However, BMI does not take into account possible differences in body composition (i.e., muscle mass, total adipose tissue and adipose distribution), meaning that a similar BMI may not reflect equivalent cardiometabolic risk profiles. Decreased height in proximal hypospadias has been shown in previous studies. Blanc et al. found that half of the men in a group of 16 with severe hypospadias and other signs of hypovirilisation were more than 5 cm below their target height.²² Örtqvist et al. found that men with proximal hypospadias had significantly decreased height compared to controls in a Swedish case-control study.²³ In this study, we had a large enough sample size to find a small but significant association even in distal hypospadias. The association with decreased adult height in our study was confounded by size at birth. However, men with hypospadias were shorter than their unexposed brothers in sibling comparison analyses and the association for men with proximal hypospadias was present both before and

after adjusting for birth size at gestational age. These results indicate that the decrease in height of men with proximal hypospadias may be due to other factors than shared heritability or growth restriction, although further investigation is needed as only 12 men with proximal hypospadias were included in adjusted sibling analyses.

This is the first study published which aims to evaluate the risk of metabolic and cardiovascular disease later in life in men with hypospadias. While our hypothesis was that the risk of both could be increased due to the decreased testosterone effect, there are further potential causes. Preeclampsia is a well-known risk factor for hypospadias in the offspring, and is also associated with metabolic and cardiovascular risk, which could mean that men with hypospadias inherit a predisposition for disease independently of the androgen function. We did not have data to control for increased maternal BMI, which is also associated with the risk of hypospadias, and could indicate hereditary risk. In sibling comparison analyses on the full population, there was no increased risk of diabetes comparing men with hypospadias to their brothers. However, the sibling comparison analyses showed equivalent effect estimates for any cardiovascular disease, indicating that the increased risk of cardiovascular disease is not caused by shared genes or environment. Our results indicate that amongst men with hypospadias, the association with type 2 diabetes mellitus may be partially due to intrauterine growth restriction, while associated malformations may partially explain the increased risk of cardiovascular disease. However, neither association can be fully explained by growth restriction or associated malformations.

There is some uncertainty about the direction of causation of the association found in many large studies between decreased

endogenous testosterone and cardiovascular disease. As hypospadias is a congenital malformation with an initial disruption in androgen levels in utero, it is an interesting model for studying temporal directionality. This study supports that there may be an underlying causal association between low testosterone and cardiovascular disease but cannot confirm it given possible alternative causes for the association measured.

4.1 | Strengths and limitations

Our population-based design using national Swedish registers presents a unique opportunity to study these associations epidemiologically on a large scale. Validity for the registers used is generally high. For most of our study period even very distal cases were treated surgically in Sweden meaning that they would be registered in the NPR, while using the MBR increases the sensitivity further. The distribution of phenotypes in our study population represents the suspected distribution, given that only penoscrotal and perineal cases are classified as proximal and for some of the time period there were no phenotype specific codes.²⁴ For those born prior to 1964, sensitivity for identifying hypospadias is lower as their diagnosis would have been registered later in childhood. This means that they may not fully represent the full patient cohort in that age bracket. For our study outcomes, the validity in the NPR for diagnosis of myocardial infarction and stroke in particular is very high, while sensitivity is low for both hypertension and obesity in the in-patient register.¹³ There is some risk of differential misclassification of these outcomes as men with hypospadias who require procedures in adulthood could receive a diagnosis which may otherwise have gone unnoticed. However, hypospadias is generally not treated or followed past 15 years of age, making the general risk of surveillance bias low. Furthermore, the effect estimates for the analysis only including stroke and myocardial infarction (i.e., high validity outcomes) indicate that the associations found cannot be explained by misclassification. For obesity, we only found a significant association with proximal hypospadias which may be overestimated due to misclassification bias. Almost all men with and without hypospadias diagnosed with hypogonadism had received a diagnosis in out-patient care, although a larger proportion of those with hypospadias had also received a diagnosis in in-patient care. Most likely, hypogonadism was a secondary diagnosis and not the reason for admission, indicating possible bias. Men with hypospadias may be more likely to be tested for and diagnosed with hypogonadism due to their condition, for instance in conjunction with in-patient urological care. However, as hypospadias has not previously been shown to be associated with hypogonadism and is not considered a risk factor, we do not think it likely that doctors would routinely connect the two except possibly in severe hypospadias.^{6,18} Similarly, men with hypospadias themselves would in most cases not suspect or seek help for hypogonadism, although we cannot rule out that having especially very proximal hypospadias may in some cases impact health-seeking behaviour, for instance when experiencing fertility issues. In Sweden, genetic and hormonal testing has only been done in recent years in severe cases of hypospadias, but most

boys with hypospadias are not routinely tested for possible hormonal dysfunction.

While the large study population and extended follow-up time allow us to study even relatively rare outcomes, such as delayed puberty, most of the study population are still comparatively young. Insufficient follow-up time could lead to an underestimation of associations, especially for cardiovascular disease which correlates strongly to age. Metabolic and cardiovascular disease at a young age may also be more likely to be related to comorbidity with other malformations, whereas the impact of decreased testosterone effect would likely become more apparent in older populations.

The use of conscription registry data with nationwide body measurements in adolescence presents a large strength of this study. Military conscription was mandatory for all men during the study period but the process for conscription varied somewhat over time. We lacked information on Swedish citizenship, which is a prerequisite for conscription, which may explain a portion of the missing data. Exclusion from conscription could occur on the basis of physical or mental illness. A physical exam was performed early in the process and abnormal genitalia was often grounds for exclusion (confirmed by conscription doctors) which may explain the differences observed in missing data. However, more men with hypospadias may have been excluded due to decreased health status which could bias our effect estimates towards the null.

We know of no significant reasons why the primary interpretations of our results could not be generalized to other populations. As the prevalence of hypospadias varies across countries, there may be some differences in the relative contribution of different underlying aetiologies in different populations, causing somewhat different associations with comorbidities.²⁵

4.2 | Conclusions and future directions

Given the large association between hypospadias and hypogonadism, increasing with severity of phenotype, we suggest hypogonadism to be considered as a differential diagnosis in adolescents and men born with hypospadias presenting with relevant signs or symptoms, and that a patient history for suspected hypogonadism or androgen-related health issues should include hypospadias. However, while the risk relative to the general male population is high, the overall risk remains low, especially amongst those with distal hypospadias. Larger scale hormone analysis is needed to more fully understand to which extent subclinical and clinical hypoandrogenism is present at different ages, as well as the relative impact of disruptions in hormone function at different molecular levels. The risk of delayed puberty and impacted growth warrant further observation in both research and clinical settings. We suggest that our results may be considered when informing adolescents with hypospadias about potential future health risks, although more research is needed on metabolic and especially cardiovascular comorbidities in men with hypospadias in older cohorts, in order to understand the respective rolls of phenotype, underlying aetiology, and pre- and postnatal development.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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AUTHOR CONTRIBUTIONS

This study was conceived by Anna Skarin Nordenvall, Lottie Phillips and Agneta Nordenskjöld. All authors contributed to the design of the study and interpretation of the results. Lottie Phillips managed the data and performed the analyses, together with Anna Skarin Nordenvall and Cecilia Lundholm. Lottie Phillips drafted the manuscript which was critically revised by all authors.

ORCID

Lottie Phillips  <https://orcid.org/0000-0002-4108-1471>

Anna Skarin Nordenvall  <https://orcid.org/0000-0003-3034-9222>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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