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How boys and testicles wander to surgery: a nationwide cohort study of surgical delay

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Abbreviations: MBR: Swedish Medical Birth Register. SAMS: Small Area of Market Studies. NPR: National Patient Register. SGA: small for gestational age, AGA: average for gestational age, LGA: large for gestational age. G: grams. HR: hazard ratio. CI: confidence interval.

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Abstract

Background: Early orchidopexy is recommended for cryptorchidism and the surgery is increasingly centralized. The objective was to describe incidence and risk factors for cryptorchidism, and to measure if long travel to treating hospital impacted the chances of timely treatment.

Methods: In this observational study, all boys born in Sweden 2001-2014 were followed in national registers to determine the incidence of cryptorchidism by levels of birth-related risk factors and social determinants. Travel time to hospital was used as the primary exposure in multivariable survival analysis, with age at surgery as main outcome.

Results: Of 748,678 boys at risk for cryptorchidism, 7351 were treated and evaluated for timing of surgery (cumulative childhood incidence 1.4%, 95% CI 1.3-1.5%). The incidence was clearly associated with prematurity and overdue pregnancy (p<0.001), low birth weight (p<0.001), and intrauterine growth restriction (p<0.001), but not with smoking (p=0.19) or maternal age (p=0.42). Each 30-minute increase in travel time was associated with a reduced probability of timely treatment (hazard ratio for being treated by age 3 adjusted for risk factors and socioeconomic determinants: 0.91 [95% CI 0.88-0.95], p<0.001). Lower income and financial support were also associated with treatment delays (adjusted hazard ratio for lowest income quintile 0.82 [95% CI 0.72-0.93], p<0.001 and for families with financial support 0.85 [95% CI 0.73-0.97], p=0.02).

Conclusions: Travel distance to treating hospital was associated with delayed treatment. “Not all those who wander are lost”, but these findings suggest a trade-off between centralization benefits and barriers of geography also in elective pediatric surgery.
Key words:
Cryptorchidism, incidence, risk factor, treatment delay, geography, socioeconomic

Summary box

What is known about the subject
Cryptorchidism should be treated early, preferably by 12-18 months of age, to avoid complications such as malignancy and infertility later in life. Risk factors for disease include prematurity and low birth weight. Pediatric anesthesia for young children is increasingly centralized to tertiary centers, while corrective surgery for older children can be performed in hospitals closer to where families live.

What this study adds
In this study, the overall incidence of disease, and the risk factor-specific incidences are presented for an entire national birth-cohort of boys. The age at surgery varied with travel time to the hospital, with less chance of timely treatment for those living further from the hospital. These results imply a trade-off between centralization benefits and geographical access to healthcare.
Introduction
Cryptorchidism is the most common genital anomaly in boys, with a reported
prevalence of 1.0-10.7%, depending on population and risk group.[1–6] Normal
testicular descent is completed in the third trimester and there is limited advancement
6 months after birth. Cryptorchid testicles are associated with impaired semen quality,
reduced fertility and increased risk of testicular malignancies later in life[7–11], and
for these reasons most guidelines and screening programs aim for diagnosis and
treatment at 6-18 months of age.[12–15] Risk factors include preterm birth, low birth
weight, and intrauterine growth restriction.[1,4,5,16,17], and genetic or environmental
factors may explain some differences in prevalence in various populations.[16]
Recent studies have suggested that maternal smoking and obesity add to this risk,
even if such studies have not considered the explanatory effect of prematurity-related
risk factors on the common pathway to disease.[18,19] A few epidemiologic studies
have claimed that socioeconomic background, rurality and insurance status are
associated with delayed treatment. [2,20,21] However, these studies were either based
on population aggregates or averages for area of residence rather than individual level
data, or have not shown any clear association with the risk for delay.[22,23]

In Sweden, like many other countries, neonatal surgery and anesthesia is increasingly
centralized to improve surgical outcomes for rare diseases and for the safety of
anesthesia to the youngest.[24] Current guidelines for the Nordic countries
recommend treatment for congenital cryptorchidism to be performed at specialized
pediatric surgery departments at 6-12 months of age,[12] but only a small minority of
boys with cryptorchidism are treated at that age.[4] It is unclear to what extent the
centralization of pediatric surgical care has become a barrier for children with less
complicated conditions living far away, and if families tend to wait until their local
hospital can help them. No study has investigated how travel time or distance to
treatment impact on delay and timing of surgery for cryptorchidism.

We performed a 14-year national register-based prospective cohort study for all boys
in Sweden, with inclusion of individual-level medical and socioeconomic risk factors.
The aim of this total population study was to determine incidence and risk factors for
cryptorchidism, and to investigate the association between travel time to hospital and
age at treatment, adjusted for medical and socioeconomic background.
Patients and Methods

Study design and study population

This was a total population study of longitudinal register data. All boys born in Sweden between January 1, 2001 until December 31, 2014 were eligible for inclusion. Study subjects were followed in national healthcare and administrative registers from birth, and they contributed until December 31 2014 unless censored due to migration, death, or outcome. Excluded were children with comorbidities that were likely to influence the standard or timing of surgical treatment (as determined by the EUROCAT list of minor malformations, n=607).[25]

Settings

The Swedish welfare system covers all citizens, and pediatric healthcare is free of charge, with no direct out-of-pocket expenses.[26] Screening for cryptorchidism was performed at birth, and at 6 and 18 months of age, as part of the regular healthy child check-ups performed by pediatricians or general practitioners with pediatric interest. Cryptorchidism is treated with an elective surgical procedure, usually performed under general anesthesia and inguinal nerve block. According to national guidelines, children younger than 12 months should be referred to a dedicated pediatric surgery unit for safe anesthesia and surgery.[12] The prevalence of cryptorchidism treatment was stable among Swedish boys throughout the study period. [4]

Primary and secondary outcomes

Primary outcome was occurrence and age at surgery for cryptorchidism, and secondary outcome was occurrence and age when diagnosis first was suspected. Date of birth was adjusted for preterm delivery by adding days up to 40 weeks pregnancy.
Age at surgery was determined by the date of surgery. The International Classification of Diseases, version 10 (ICD-10) and Nordic Medico-Statistical Committee Classification of Surgical Procedures (NOMESCO-CSP) were used throughout the study period for coding of diseases and procedures.[27] Cryptorchidism was defined by any ICD-10 code Q53.0-9 and Q55.0-1 and surgery for cryptorchidism was defined by any of the procedures KFH00, KFH10, JAH01, KFC00, KFC96 or KFD00 added to the ICD-code.

Exposure, risk factors and socioeconomic determinants

Primary exposure was travel time to treating hospital. The most time-efficient way from the population centroid (age 0-18 years) of each patient’s area of residence (Small Area of Market Studies, SAMS) at the time of birth to the geo-coordinates of the treating hospital was estimated, considering speed limitations, stop signals, left turns and right turns as they were at the year of birth, and reported in minutes as a continuous variable. Medical risk factors were length of pregnancy (<32 weeks, 32-36 weeks, 37-41 weeks, >42 weeks), birth weight (<1000g, 1000-1499g, 1500-2499g, 2500-4200g, >4200g), size for gestational age (small, average or large for gestational age), maternal age and smoking status during pregnancy (no smoking, 1-9 cigarettes/day or >9/day). Socioeconomic determinants included educational level of parents, unemployment, income, social transfers, and place of birth. The highest achieved education within the family was categorized either as the completion of compulsory school (<10 years), high school (<13 years) or higher education (>12 years). Unemployment was defined as any parent being registered in the Swedish Unemployment Service one year prior to inclusion. Income was determined by the sum of the parents’ income after taxations and transfers the year prior to inclusion, to
avoid influence of parental leave on income, and families were categorized in annual
income quintiles to adjust for inflation and shifts in taxation and regulations. Social
transfers included any governmental financial support the year prior to inclusion.
Parents were categorized as being born either in Sweden or elsewhere, and the child
could have two, one, or no Swedish-born parents.

Data sources and data validity
The study population was identified in the Swedish Medical Birth Register
(MBR).[28] Birth characteristics were collected from the MBR, and medical records
were retrieved from the Swedish National Patient Register (NPR). MBR covers all
births in Sweden and NPR covers >99% of inpatient care and 80-86% of specialized
outpatient care including day surgery in private and public hospitals during the study
period.[29,30] The Swedish Multi-Generation Register was used to identify parents in
the cohort, and socioeconomic information and parental place of residence were
retrieved from the Longitudinal Integration Database for Health Insurance and Labour
Market Studies (LISA).[31,32] The Register of the Total Population (Statistics
Sweden) provided information on parents’ migration status.[33] Annual data on the
Swedish roads and infrastructure were collected from the Sweden’s National Road
Database.[34]

Statistical analysis
Descriptive statistics presents the cohort's independent variables as distributed by
levels of primary exposure. The cumulative incidence and timing of cryptorchidism
diagnosis and treatment were reported as percentages and presented in Kaplan-Meier
curves and assessed by log-rank test. P-values obtained by F-tests assessed the overall
the contribution of each categorical variable included in the regression models. Hazard ratios (HR) of each risk factor, adjusted for study year and socioeconomic determinants, were obtained by Cox regression and reported with 95% confidence intervals (CI). As primary exposure was applicable only for subjects with surgical treatment, a Cox regression model was designed to assess for treatment delay in the sub-cohort of treated children, with adjustment for year of birth, risk factors and socioeconomic determinants. Time of censoring was set to 3 years of age; an age cut-off chosen as cases of congenital cryptorchidism should have been identified and treated and acquired cryptorchidism should still have limited influence. To assess robustness of results, alternative censoring at 2 and 5 years of age was applied as well. Similarly, travel time was also categorized and included in the model on the nominal scale as a sensitivity analysis of main associations. All multivariable cox regression models were stratified on healthcare region of residence, in order to adjust for clustered data.

Software

ArcGis® 10.2, Environmental Systems Research Institute (ESRI) of Redlands, California was used to calculate travel times and STATA/SE® 14.1 for Windows was used for statistics.[35]
Results

Cumulative incidence and timing surgery

Of 748,678 boys, 7351 were treated for cryptorchidism and evaluated for timing of surgery (Figure 1). The cumulative incidence of surgically treated cryptorchidism in the oldest birth cohort (2001-2002, followed until 14 years age) was 1.4% (95% CI 1.3-1.5%). The estimated travel time from place of residence to treating hospital was 36 minutes in mean (standard deviation 58 minutes) and 20 minutes in median (IQR 11-38 minutes). More children traveled longer to the treatment later in the study period (eTable 1), and there was also a trend towards earlier diagnosis and treatment later in the study period, in particular after the introduction of national guidelines in 2007 (p<0.001, Figure 2A and eFigure 1).

Risk factors for cryptorchidism

Prematurity and overdue pregnancy were associated with increased incidence of disease (p<0.001, Figure 2B), as were low birth weight (p<0.001, Figure 2C) and intrauterine growth restriction (p<0.001, Figure 2D). Maternal age and smoking status were not associated with the incidence (p=0.42 and p=0.19). These results were robust in bivariate models with adjustment for year of birth (eFigure 2), and in a multivariable model with adjustment for socioeconomic confounders (Figure 3).

Association between travel distance and timing of treatment

The unadjusted association between travel distance and timing of treatment is presented in eFigure 3. Bivariate associational estimates of travel time and of each socioeconomic variable, with adjustment for year of birth only, are presented in eFigure 4. In the multivariable analysis, the probability of timely surgery decreased
by each 30-minute increase in travel time (adjusted HR 0.91 (0.88-0.95), p<0.001; Figure 4). Whereas high income (p=0.001) and absence of social security support (p=0.02) were associated with increased rate of surgical treatment before age of 3 years, no such associations were seen by levels of education, employment, or parental migration status (Figure 4). The association between travel distance to hospital and treatment age did not change substantially in any of the performed sensitivity analyses (Appendix page 7-8, eFigure 5-6).

Discussion

In this national birth-cohort study of all Swedish-born boys, cumulative incidences of cryptorchidism were determined for established risk factors of disease. The incidence by 14 years of age was 1.4%. Travel distance to the treating hospital was associated with treatment delay, also when medical and socioeconomic factors were adjusted for.

These results underline the considerable national public health implications of screening and treating cryptorchidism in boys, and confirm a remarkable increase in risk for boys born prematurely, with low birth weight or with diverging size for gestational age. The association between travel time and delayed treatment may appear counter-intuitive for a non-emergent condition like cryptorchidism. It is possible, however, that some parents could hesitate to accept a long-distance referral with their infant child, or that the result reflects a guideline-awareness gradient within the healthcare system. Regardless, the association delineates a trade-off between centralization benefits and geographical access in elective surgery for children. Meanwhile surgical care in general, and pediatric surgery in particular, is increasingly centralized, these findings address potential problems with this transition.
The incidences and risk stratification by medical birth determinants reported here are in line with previous studies.[1–6,16,17] However, maternal smoking during pregnancy did not add to the risk in our analysis, and the recently reported association of smoking on cryptorchidism risk may have been mediated by imbalances in established birth-related risk factors.[19] Whereas a few earlier studies have reported associations between rural area of residence and treatment delays in cryptorchidism[2,20], and one study has indicated that the general risk of increasing waiting-times for pediatric surgery for patients living further from hospital[36], this is the first study to investigate associations with the patient’s estimated travel time to elective care with adjustment for individual-level socioeconomic determinants. Interestingly, increasing travel distance was not associated with adverse outcome in pediatric appendicitis, which may reflect the generally shorter distances to emergency hospitals.[37] A few studies of cryptorchidism, in various healthcare systems and populations, have reported treatment delays for children with worse insurance status or lower average income and education in neighborhood area of residence.[2,21] This effect seems context-specific, as indicated by a Canadian study showing that average deprivation status and income level in area of residence did not associate with treatment delays in pediatric surgery in general.[36] When multiple individual-level social determinants of health are adjusted for, the impact of income on the probability to be treated timely seems valid also in Sweden. Overall, however, socioeconomic background seems to be a relative week predictor of treatment delay in Sweden.

Limitations
This study was based on individual-level healthcare data and administrative records of a national population of children with free access to care. Consequently, the risk for selection bias due to a diversified healthcare system or financial barriers was reduced to a minimum. However, residual selection bias due to referral propensity based on age cannot be ruled out. Further, distinction between congenital and acquired cryptorchidism could not be done, which relates to the interpretation of the cumulative incidence. Due to the study design, causality cannot be claimed and associations could be susceptible to unmeasured confounding. The accuracy of the administrative registers is expected to be high, yet it is possible that a hidden skewness exists, and most likely such effect would dilute the observed effects. A strength of this study is that travel time to the treating hospital was measured continuously for each treated individual in this cohort. Travel time may be a more realistic measure of geographic access than measures of distance. Yet these are estimates, not exact travel times, as the trip originated at the population centroid of the area of residence rather than the exact home address. Further, a bias may have been introduced in these calculations as all families were expected to have access to a motor vehicle for transportation, even if this might have varied between socioeconomic strata.

**Conclusion**

This study confirms that the cryptorchidism incidence among boys is tightly linked to prematurity, low birth weight, and size for gestational age. It is the first study to measure the association between travel time to hospital and access to timely treatment for elective surgery in children, with adjustment for socioeconomic determinants on
individual level. We conclude that increased travel time was associated with delayed treatment.

**Ethical considerations and reporting statement**

Approval to access healthcare data of the cohort was obtained from the Ethical Review Board in Lund (2014/791 and 2015/429) and ethical approval to access individual level socioeconomic and geographic determinants on parents was obtained from the Central Ethical Review Board in Stockholm (Ö 19-2015), and by ethical vetting at Statistics Sweden. The study was reported in compliance with the STROBE guidelines.[38] It was not possible or appropriate to involve patients and public in the research process.

**Author contribution statement:**

Dr. Omling and Dr. Hagander planned, designed and conceptualized the study, applied for ethical approval, acquisitioned data, performed statistical analyses, interpreted results, drafted and approved the manuscript.

Professor Björk planned, designed and conceptualized the study, applied for ethical approval, performed statistical analyses, interpreted results, and approved the final manuscript.

Dr. Bergbrant planned, designed and conceptualized the study, applied for ethical approval, acquisitioned data, interpreted results, and approved the final manuscript.

Associate Professor Persson conceptualized the study, performed geographic data analysis, interpreted results and approved the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
**Conflict of interest statement**

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**Transparency declaration**

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

**Data sharing**
Data is not available for public access. Please contact the corresponding author with requests regarding data access.
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Figure legends:

Figure 1. Inclusion and exclusion of Swedish children diagnosed and treated for cryptorchidism.

Figure 2. Cumulative incidence of surgery for cryptorchidism among 748,678 Swedish boys, by year of birth and risk factors. Follow-up was until end of 2014. Note different scales on vertical axis in Figures A and B-D. A. Age at treatment for 2-year birth cohorts. There was a shift towards earlier treatment after the introduction of Nordic guidelines in 2007. B. By birth week. C. By birth weight. D. By size for gestational age.

Figure 3. Childhood incidence (age 0-14 years) and hazard ratios of surgery for cryptorchidism, by medical risk factors. Effect estimates from multivariable Cox regression model adjusted for year of birth, and socioeconomic determinants including highest education, unemployment, income, financial support and number of parents born in Sweden.

Figure 4. Hazard ratio of having had surgery at 3 years of age among boys treated for cryptorchidism, by travel time to treating hospital and socioeconomic determinants. Multivariable Cox regression model adjusted for year of birth and medical risk factors (birth week, size for gestational age, maternal smoking and age).
| Treated for cryptorchidism by age 14 | Incidence n (%) | Relative incidence Lower | Relative incidence Higher | Hazard ratio (95% confidence interval) | P-value |
|--------------------------------------|-----------------|--------------------------|--------------------------|----------------------------------------|---------|
| **Length of pregnancy (weeks)**     |                 |                          |                          |                                        |         |
| <32                                  | 182 (2.6)       |                          |                          | 2.36 (1.97 to 2.82)                   | <0.001  |
| 32-36                                | 494 (1.3)       |                          |                          | 1.32 (1.20 to 1.46)                   |         |
| >41                                  | 646 (1.1)       |                          |                          | 1.18 (1.09 to 1.29)                   |         |
| **Size for gestational age**         |                 |                          |                          |                                        | <0.001  |
| Small                                | 355 (2.2)       |                          |                          | 2.10 (1.87 to 2.37)                   |         |
| Average                              | 6684 (1.0)      |                          |                          | 1                                      |         |
| Large                                | 312 (1.2)       |                          |                          | 1.34 (1.19 to 1.51)                   |         |
| **Maternal smoking during pregnancy**|                 |                          |                          |                                        | 0.14    |
| No smoking                           | 6142 (1.0)      |                          |                          | 1                                      |         |
| 1-9 cigarettes per day               | 471 (1.1)       |                          |                          | 1.10 (0.99 to 1.22)                   |         |
| >9 cigarettes per day                | 188 (1.1)       |                          |                          | 1.07 (0.92 to 1.26)                   |         |
| **Maternal age at birth (years)**    |                 |                          |                          |                                        | 0.61    |
| <20                                  | 130 (1.1)       |                          |                          | 1.08 (0.86 to 1.36)                   |         |
| 20-24                                | 971 (1.0)       |                          |                          | 0.97 (0.88 to 1.05)                   |         |
| 25-39                                | 2149 (1.0)      |                          |                          | 0.97 (0.91 to 1.03)                   |         |
| 30-34†                               | 2575 (1.0)      |                          |                          | 1                                      |         |
| 35-39                                | 1291 (1.0)      |                          |                          | 0.99 (0.92 to 1.06)                   |         |
| >39                                  | 235 (0.9)       |                          |                          | 0.90 (0.78 to 1.04)                   |         |

* Reference category chosen as baseline in the regression analysis.

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| Treated for cryptorchidism at age 3 years | Timing of treatment | Hazard ratio [95% confidence interval] | P-value |
|------------------------------------------|---------------------|----------------------------------------|---------|
| Travel time to treating hospital         |                     |                                        |         |
| By each 30-minute increase               | Later               | 0.91 (0.88 to 0.95)                    | <0.001  |
| Education (years)                        |                     |                                        |         |
| >12<sup>a</sup>                         |                     |                                        | 0.64    |
| 10-12                                   |                     |                                        | 0.97 (0.90 to 1.04) |
| <10                                     |                     |                                        | 0.99 (0.82 to 1.20) |
| Employment                               |                     |                                        | 0.19    |
| Yes<sup>a</sup>                          |                     |                                        |         |
| Unemployment                             |                     |                                        | 0.93 (0.84 to 1.03) |
| Income (quintiles)                       |                     |                                        | <0.001  |
| Q5, highest income<sup>a</sup>           |                     |                                        |         |
| Q4                                       |                     |                                        | 0.88 (0.79 to 0.97) |
| Q3                                       |                     |                                        | 0.80 (0.72 to 0.89) |
| Q2                                       |                     |                                        | 0.90 (0.81 to 1.00) |
| Q1, lowest income                        |                     |                                        | 0.82 (0.72 to 0.93) |
| Financial support                        |                     |                                        | 0.02    |
| No support<sup>a</sup>                   |                     |                                        |         |
| Support                                  |                     |                                        | 0.85 (0.73 to 0.97) |
| Parents born in Sweden                   |                     |                                        | 0.46    |
| Two<sup>a</sup>                          |                     |                                        |         |
| One                                      |                     |                                        | 1.06 (0.96 to 1.17) |
| None                                     |                     |                                        | 1.04 (0.93 to 1.16) |

<sup>a</sup> Reference category chosen as baseline in the regression analysis.
Online-only supplement

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| Boys at risk | Cryptorchidism Surgery, n(%) | Travel time to treating hospital (minutes)* |
|-------------|-----------------------------|---------------------------------------------|
| Total       | 748,678                     | 7351                                        |
|             | 5006                         | 1367                                        |
|             | 387                          | 579                                         |
| **Year of birth** |                               |                                             |
| 2001-2002   | 93,891 (12.5)                | 1272 (17.3)                                |
| 2003-2004   | 100,891 (13.5)               | 1343 (18.3)                                |
| 2005-2006   | 103,832 (13.9)               | 1168 (15.9)                                |
| 2007-2008   | 108,568 (14.5)               | 1292 (17.6)                                |
| 2009-2010   | 113,669 (15.2)               | 1101 (15.0)                                |
| 2011-2012   | 112,712 (15.1)               | 943 (12.8)                                 |
| 2013-2014   | 115,104 (15.4)               | 232 (3.2)                                  |
| **Birth weight, g** |                               |                                             |
| <1000       | 2264 (0.3)                   | 79 (1.1)                                   |
| 1000-1499   | 3294 (0.4)                   | 112 (1.5)                                  |
| 1500-2499   | 23,748 (3.2)                 | 372 (5.1)                                  |
| 2500-4199   | 62,111,158 (83.0)            | 5796 (78.8)                                |
| 4200-      | 96,819 (12.9)                | 970 (13.2)                                 |
| Missing data| 1438 (0.2)                   | 22 (0.3)                                   |
| **Size for gestational week** |                               |                                             |
| Small (SGA) | 16,048 (2.1)                 | 355 (4.8)                                  |
| Average (AGA)| 706,891 (94.4)               | 6684 (90.3)                                |
| Large (LGA) | 25,739 (3.4)                 | 312 (4.2)                                  |
| Missing data| -                            | -                                           |
| **Length of pregnancy, w** |                               |                                             |
| <32         | 7121 (1.0)                   | 192 (2.5)                                  |
| 32-36       | 38,649 (5.2)                 | 494 (6.7)                                  |
| 37-41       | 64,795 (86.1)                | 6021 (81.9)                                |
| 42-         | 57,796 (7.7)                 | 646 (8.8)                                  |
| Missing data| 315 (0.0)                    | 8 (0.1)                                    |
| **Mother age, year** |                               |                                             |
| <20         | 11,779 (1.6)                 | 130 (1.8)                                  |
| 20-24       | 94,900 (12.7)                | 971 (13.2)                                 |
| 25-29       | 222,375 (29.7)               | 2149 (29.2)                                |
| 30-34       | 261,366 (34.9)               | 2575 (35.0)                                |
| 35-39       | 131,080 (17.5)               | 1291 (17.6)                                |
| >39         | 27,174 (3.6)                 | 235 (3.2)                                  |
| Missing data| 4                            | -                                           |
| **Mother smoking** |                               |                                             |
| No          | 642,434 (85.8)               | 6142 (83.5)                                |
| 1-9 cigarettes/d | 42,618 (5.7)                 | 471 (6.4)                                  |
| >9 cigarettes/d | 16,562 (2.2)                 | 188 (2.6)                                  |
| Missing data| 47,062 (6.7)                 | 550 (7.5)                                  |
| **Parents’ education** |                               |                                             |
| >12 years   | 413,451 (55.2)               | 3842 (52.3)                                |
| 10-12 years | 270,838 (36.2)               | 2863 (38.9)                                |
| <10 years   | 26,082 (3.5)                 | 279 (3.8)                                  |
| Missing data| 38,306 (5.1)                 | 367 (5.0)                                  |
| **Unemployed parents** |                               |                                             |
| No          | 624,497 (83.4)               | 6179 (84.1)                                |
| Yes         | 98,932 (13.2)                | 934 (12.7)                                 |
| Missing data| 25,249 (3.4)                 | 238 (3.2)                                  |
| **Income, quintile** |                               |                                             |
| Q5 (highest income) | 133,171 (17.8)               | 1457 (19.8)                                |
| Q4          | 133,173 (17.8)               | 1354 (18.4)                                |
| Q3          | 133,167 (17.8)               | 1399 (19.0)                                |
| Q2          | 133,162 (17.8)               | 1421 (19.3)                                |

*Table 1. Swedish-born boys treated for cryptorchidism (2001-2014), by risk factors and socioeconomic determinants (left) and travel time to treating hospital (right).
eFigure 1. Cumulative incidence of cryptorchidism (diagnosis) among 748,678 Swedish boys, by two-year birth cohorts (2001-2014). Follow-up is until end of 2014.
| Cryptorchidism treatment | Yes n (%) | Relative incidence Lower | Relative incidence Higher | Hazard ratio (95% confidence interval) | P-value |
|--------------------------|-----------|--------------------------|--------------------------|----------------------------------------|---------|
| Birth weight (gram)      |           |                          |                          |                                        | <0.001  |
| ELBW<sup>a</sup> (<1000 gram) | 79 (3.5)  |                          |                          | 3.94 (3.15 to 4.92)                   |         |
| VLBW<sup>b</sup> (1000-1499 gram) | 112 (3.4) |                          |                          | 3.70 (3.07 to 4.46)                   |         |
| LBW<sup>c</sup> (1500-2499 gram) | 372 (1.6) |                          |                          | 1.69 (1.52 to 1.88)                   |         |
| Normal (2500-4199 gram)  | 5796 (0.9) |                          |                          | 1                                     |         |
| Heavy (≥ 4200 gram)      | 970 (1.0)  |                          |                          | 1.06 (0.99 to 1.13)                   |         |
| Size for gestational age |           |                          |                          |                                        | <0.001  |
| Small (SGA)              | 355 (2.2)  |                          |                          | 2.38 (2.14 to 2.65)                   |         |
| Average (AGA) (ref)      | 6684 (0.9) |                          |                          | 1                                     |         |
| Large (LGA)              | 312 (1.2)  |                          |                          | 1.26 (1.13 to 1.42)                   |         |
| Length of pregnancy      |           |                          |                          |                                        | <0.001  |
| <32 weeks                | 182 (2.6)  |                          |                          | 2.77 (2.39 to 3.21)                   |         |
| 32-36 weeks              | 494 (1.3)  |                          |                          | 1.36 (1.24 to 1.49)                   |         |
| 37-41 weeks (ref)        | 6021 (0.9) |                          |                          | 1                                     |         |
| >42 weeks                | 646 (1.1)  |                          |                          | 1.19 (1.10 to 1.29)                   |         |
| Maternal smoking         |           |                          |                          |                                        | 0.13    |
| No smoking (ref)         | 6142 (1.0) |                          |                          | 1                                     |         |
| 1-9 cigarettes/d         | 471 (1.1)  |                          |                          | 1.09 (0.99 to 1.19)                   |         |
| >9 cigarettes/d          | 6801 (1.0) |                          |                          | 1.08 (0.93 to 1.25)                   |         |
| Age of mother (years)    |           |                          |                          |                                        | 0.35    |
| <20                      | 130 (1.1)  |                          |                          | 1.08 (0.91 to 1.29)                   |         |
| 20-24                    | 971 (1.0)  |                          |                          | 1.05 (0.98 to 1.14)                   |         |
| 25-29                    | 2149 (1.0) |                          |                          | 0.99 (0.93 to 1.04)                   |         |
| 30-34 (ref)              | 2575 (1.0) |                          |                          | 1                                     |         |
| 35-39                    | 1291 (1.0) |                          |                          | 1.02 (0.95 to 1.09)                   |         |
| >39                      | 235 (0.9)  |                          |                          | 0.92 (0.81 to 1.06)                   |         |
| Education (years)        |           |                          |                          |                                        | 0.002   |
| >12 (ref)                | 3842 (0.9) |                          |                          | 1                                     |         |
| 10-12                    | 2863 (1.1) |                          |                          | 1.08 (1.02 to 1.13)                   |         |
| <10                      | 279 (1.1)  |                          |                          | 1.15 (1.02 to 1.30)                   |         |
| Employment               |           |                          |                          |                                        | 0.53    |
| Yes (ref)                | 6179 (1.0) |                          |                          | 1                                     |         |
| Unemployment             | 934 (0.9)  |                          |                          | 1.02 (0.95 to 1.10)                   |         |
| Income (quintiles)       |           |                          |                          |                                        | 0.15    |
| Q5, highest income (ref) | 1440 (1.1) |                          |                          | 1                                     |         |
| Q4                       | 1421 (1.1) |                          |                          | 0.98 (0.91 to 1.05)                   |         |
| Q3                       | 1399 (1.1) |                          |                          | 0.96 (0.90 to 1.04)                   |         |
| Q2                       | 1354 (1.0) |                          |                          | 0.93 (0.87 to 1.01)                   |         |
| Q1, lowest income        | 1457 (1.1) |                          |                          | 1.02 (0.95 to 1.10)                   |         |
| Financial support        |           |                          |                          |                                        | <0.001  |
| No support (ref)         | 6381 (1.0) |                          |                          | 1                                     |         |
| Support                  | 779 (1.1)  |                          |                          | 1.15 (1.07 to 1.24)                   |         |
| Parents born in Sweden   |           |                          |                          |                                        | <0.001  |
| Two (ref)                | 5063 (1.0) |                          |                          | 1                                     |         |
| One                      | 962 (0.9)  |                          |                          | 1.06 (0.99 to 1.14)                   |         |
| None                     | 1324 (1.1) |                          |                          | 1.37 (1.29 to 1.46)                   |         |

<sup>a</sup>Extremely low birth weight. <sup>b</sup>Very low birth weight. <sup>c</sup>Low birth weight.

eFigure 2. Childhood Incidence of cryptorchidism, hazard ratio by risk factors and socioeconomic variables. Bivariate logistic models, adjusted for year of birth.
eFigure 3. Timing of surgery among children treated for cryptorchidism. The cumulative proportion, by non-adjusted levels of travel time to hospital. Children born in Sweden 2001-2014, followed until 5 years of age.
| Travel time to treating hospital (minutes) | Treated at age 3, n (%) | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|------------------------------------------|-------------------------|--------------------|----------------------------------------|---------|
| By each 30-minutes increase               |                         |                    | 0.91 (0.88 to 0.95)                    | <0.001  |
| By categories                            |                         |                    |                                        |         |
| <30 (ref)                                | 2946 (58.8)             | Later              | 1                                      |         |
| 30-59                                    | 736 (53.8)              |                    | 0.84 (0.77 to 0.91)                    | <0.001  |
| 60-89                                    | 207 (53.5)              |                    | 0.72 (0.62 to 0.82)                    |         |
| >90                                      | 364 (62.9)              |                    | 0.84 (0.76 to 0.94)                    |         |
| Education (years)                        |                         |                    |                                        | 0.001   |
| >12 (ref)                                | 2319 (60.4)             |                    | 1                                      |         |
| 10-12                                    | 1549 (54.1)             |                    | 0.90 (0.84 to 0.96)                    |         |
| <10                                      | 153 (54.8)              |                    | 0.82 (0.70 to 0.97)                    |         |
| Full employment                          |                         |                    |                                        | 0.003   |
| Yes (ref)                                | 3564 (57.7)             |                    | 1                                      |         |
| No                                       | 554 (59.3)              |                    | 0.87 (0.80 to 0.95)                    |         |
| Income (quintiles)                       |                         |                    |                                        | <0.001  |
| Q5, highest income (ref)                 | 855 (59.4)              |                    | 1                                      |         |
| Q4                                       | 817 (57.5)              |                    | 0.87 (0.79 to 0.95)                    |         |
| Q3                                       | 801 (57.3)              |                    | 0.79 (0.72 to 0.87)                    |         |
| Q2                                       | 789 (56.4)              |                    | 0.86 (0.78 to 0.95)                    |         |
| Q1, lowest income                        | 821 (56.4)              |                    | 0.76 (0.69 to 0.84)                    |         |
| Financial support                        |                         |                    |                                        | <0.001  |
| No support (ref)                         | 3725 (58.4)             |                    | 1                                      |         |
| Support                                  | 412 (52.9)              |                    | 0.81 (0.73 to 0.90)                    |         |
| Parents born in Sweden                   |                         |                    |                                        | 0.15    |
| Two (ref)                                | 2859 (56.5)             |                    | 1                                      |         |
| One                                      | 597 (62.1)              |                    | 1.07 (0.98 to 1.17)                    |         |
| None                                     | 802 (60.6)              |                    | 0.96 (0.89 to 1.04)                    |         |

**eFigure 4.** Relative incidence of treatment for cryptorchidism before 3 years of age, and hazard ratio by travel time to treating hospital and socioeconomic determinants. Bivariate Cox regression model adjusted for year of birth, without adjustment for risk factors.
Sensitivity analysis of main associations
The estimated hazard ratio for treatment by levels of travel time did not change substantially when travel time was presented as categories on the nominal scale (<30 minutes travel time being reference, the adjusted HR for 30-59 minutes travel time: 0.82 [95% CI 0.75 to 0.90]; adjusted HR for 60-89 minutes: 0.72 [95% CI 0.62 to 0.83]; and adjusted HR for 90 minutes or more: 0.84 [95% CI 0.74 to 0.95], p<0.001 for overall variable contribution). Later in the study period, more children had a longer travel time to hospital (eTable 1). Robustness of the results by the introduction of Nordic guidelines in 2007 were therefore tested by splitting the cohort in two, based on year of birth (2001-2006 and 2007-2014). This resulted in similar hazard ratios (by each 30-minute increase in travel time for children born 2001-2006; adjusted HR 0.90 [95% CI 0.83 to 0.96], p=0.003, and for children born 2007-2014; adjusted HR 0.92 [95% CI 0.88 to 0.96], p<0.001). The main association was also robust to changes in age cut-off in the survival analysis (eFigures 5 and 6). In fact, the relative incidence of being treated was even higher at age 2 years (treatment rate by each 30-minute increase in travel time: adjusted HR 0.87 [95% CI 0.83 to 0.91], p<0.001) and remained at age 5 years (adjusted HR 0.96 [95% CI 0.92 to 1.00], p=0.03).

| Treated for cryptorchidism at age 2 | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|-------------------------------------|---------------------|---------------------------------------|---------|
|                                     | Later               | Earlier                               |         |
| Travel time to hospital (minutes)   |                     |                                       |         |
| By each 30-minute increase          |                     | 0.87 (0.83 to 0.91)                   | <0.001  |
| Education (years)                   |                     |                                       |         |
| >12 (ref)                           |                     | 1                                     | 0.48    |
| 10-12                               |                     | 0.95 (0.87 to 1.03)                   |         |
| <10                                 |                     | 0.96 (0.77 to 1.21)                   |         |
| Employment                          |                     |                                       |         |
| Yes (ref)                           |                     | 1                                     | 0.19    |
| Unemployment                        |                     | 0.92 (0.81 to 1.04)                   |         |
| Income (quintiles)                  |                     |                                       | <0.001  |
| Q5, highest income (ref)            |                     | 1                                     |         |
| Q4                                  |                     | 0.84 (0.74 to 0.94)                   |         |
| Q3                                  |                     | 0.72 (0.64 to 0.82)                   |         |
| Q2                                  |                     | 0.85 (0.75 to 0.96)                   |         |
| Q1, lowest income                   |                     | 0.78 (0.67 to 0.91)                   |         |
| Financial support                   |                     |                                       |         |
| No support (ref)                    |                     | 1                                     | 0.02    |
| Support                             |                     | 0.81 (0.68 to 0.97)                   |         |
| Parents born in Sweden              |                     |                                       |         |
| Two (ref)                           |                     | 1                                     | 0.64    |
| One                                 |                     | 1.05 (0.93 to 1.18)                   |         |
| None                                |                     | 1.05 (0.92 to 1.19)                   |         |

eFigure 5. Sensitivity analysis. Hazard ratio of treatment for cryptorchidism before 2 years of age, by travel time to treating hospital and socioeconomic determinants. Multivariable Cox regression model adjusted for year of birth and risk factors (birth week, size for gestational age, maternal smoking and age). Children born 2001-2014, followed 24 months from birth.
### Treated for cryptorchidism at age 5

| Travel time to hospital (minutes) | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|----------------------------------|---------------------|----------------------------------------|---------|
| By each 30-minute increase       | Later               | 0.95 (0.92 to 0.98)                    | 0.001   |
|                                  | Earlier             |                                        |         |

| Education (years)                | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|----------------------------------|---------------------|----------------------------------------|---------|
| >12 (ref)                        |                    | 1                                      |         |
| 10-12                            |                    | 0.99 (0.93 to 1.06)                    |         |
| <10                              |                    | 0.95 (0.80 to 1.12)                    |         |

| Employment                       | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|----------------------------------|---------------------|----------------------------------------|---------|
| Yes (ref)                        |                    |                                        | 0.20    |
| Unemployment                     |                    | 0.94 (0.86 to 1.03)                    |         |

| Income (quintiles)               | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|----------------------------------|---------------------|----------------------------------------|---------|
| Q5, highest income group (ref)   |                    | 1                                      |         |
| Q4                               |                    | 0.90 (0.83 to 0.99)                    |         |
| Q3                               |                    | 0.83 (0.75 to 0.91)                    |         |
| Q2                               |                    | 0.89 (0.80 to 0.98)                    |         |
| Q1, lowest income                |                    | 0.88 (0.78 to 0.98)                    |         |

| Financial support                | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|----------------------------------|---------------------|----------------------------------------|---------|
| No support (ref)                 |                    | 1                                      |         |
| Support                          |                    | 0.84 (0.74 to 0.95)                    | 0.005   |

| Parents born in Sweden           | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|----------------------------------|---------------------|----------------------------------------|---------|
| Two (ref)                        |                    | 1                                      | 0.63    |
| One                              |                    | 1.04 (0.95 to 1.14)                    |         |
| None                             |                    | 1.03 (0.94 to 1.14)                    |         |

**eFigure 6. Sensitivity analysis.** Hazard ratio of treatment for cryptorchidism before 5 years of age, by travel time to treating hospital and socioeconomic determinants. Multivariable Cox regression model adjusted for year of birth and risk factors (birth week, size for gestational age, maternal smoking and age). Children born 2001-2014, followed 60 months from birth.
How boys and testicles wander to surgery: a nationwide cohort study of surgical delay in Sweden

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How boys and testicles wander to surgery:
a nationwide cohort study of surgical delay in Sweden

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Abbreviations: MBR: Swedish Medical Birth Register. SAMS: Small Area of Market Studies. NPR: National Patient Register. SGA: small for gestational age, AGA: average for gestational age, LGA: large for gestational age. G: grams. HR: hazard ratio. CI: confidence interval.

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Abstract

Background: Early orchidopexy is recommended for cryptorchidism and the surgery is increasingly centralized. The objectives were to determine the incidence, risk factors, and if distance to treating hospital impacted on timely treatment of cryptorchidism.

Methods: In this observational study, all boys born in Sweden 2001-2014 were followed in national registers to determine the incidence of cryptorchidism by levels of birth-related risk factors and social determinants. Travel time to hospital was used as the primary exposure in multivariable survival analysis, with age at surgery as main outcome.

Results: Of 748,678 boys at risk for cryptorchidism, 7351 were treated and evaluated for timing of surgery (cumulative childhood incidence 1.4%, 95% CI 1.3-1.5%). The incidence was clearly associated with prematurity and overdue pregnancy (p<0.001), low birth weight (p<0.001), and intrauterine growth restriction (p<0.001), but not with smoking (p=0.19) or maternal age (p=0.42). Each 30-minute increase in travel time was associated with a reduced probability of timely treatment (hazard ratio for being treated by age 3 adjusted for risk factors and socioeconomic determinants: 0.91 [95% CI 0.88-0.95], p<0.001). Lower income and financial support were also associated with treatment delays (adjusted hazard ratio for lowest income quintile 0.82 [95% CI 0.72-0.93], p<0.001 and for families with financial support 0.85 [95% CI 0.73-0.97], p=0.02).

Conclusions: Travel distance to treating hospital was associated with delayed treatment. “Not all those who wander are lost”, but these findings suggest a trade-off between centralization benefits and barriers of geography also in elective pediatric surgery.
**Key words:**
Cryptorchidism, incidence, risk factor, treatment delay, geography, socioeconomic

**Summary box**

**What is known about the subject**
Cryptorchidism should be treated early, preferably before 18 months of life, to avoid complications such as malignancy and infertility later in life. Risk factors for disease include prematurity and low birth weight. Pediatric anesthesia for young children is increasingly centralized to tertiary centers, while corrective surgery for older children can be performed in hospitals closer to where families live.

**What this study adds**
In this study, the overall incidence of disease, and the risk factor-specific incidences are presented for an entire national birth-cohort of boys. The age at surgery varied with travel time to the hospital, with less chance of timely treatment for those living further from the hospital. These results imply a trade-off between centralization benefits and geographical access to healthcare.
**Introduction**
Cryptorchidism is the most common genital anomaly in boys, with a reported prevalence of 1.0-10.7%, depending on population and risk group.[1–6] Normal testicular descent is completed in the third trimester and there is limited advancement 6 months after birth. Cryptorchid testicles are associated with impaired semen quality, reduced fertility and increased risk of testicular malignancies later in life[7–11], and for these reasons most guidelines and screening programs aim for diagnosis and treatment at 6-18 months of age.[12–15] Risk factors include preterm birth, low birth weight, and intrauterine growth restriction [1,4,5,16,17], and genetic or environmental factors may explain some differences in prevalence in various populations.[16] Recent studies have suggested that maternal smoking and obesity add to this risk, even if such studies have not considered the explanatory effect of prematurity-related risk factors on the common pathway to disease.[18,19] A few epidemiologic studies have claimed that socioeconomic background, rurality and insurance status are associated with delayed treatment. [2,20,21] However, these studies were either based on population aggregates or averages for area of residence rather than individual level data, or have not shown any clear association with the risk for delay.[22–24]

In Sweden, like many other countries, neonatal surgery and anesthesia is increasingly centralized to improve surgical outcomes for rare diseases and for the safety of anesthesia to the youngest.[25] Current guidelines for the Nordic countries recommend treatment for congenital cryptorchidism to be performed at specialized pediatric surgery departments at 6-12 months of age,[12] but only a small minority of boys with cryptorchidism are treated at that age.[4] It is unclear to what extent the centralization of pediatric surgical care has become a barrier for children with less complicated conditions living far away, and if families tend to wait until their local
hospital can help them. No study has investigated how travel time or distance to
treatment impact on delay and timing of surgery for cryptorchidism.

We performed a 14-year national register-based prospective cohort study for all boys
in Sweden, with inclusion of individual-level medical and socioeconomic risk factors.
The aim of this total population study was to determine incidence and risk factors for
cryptorchidism, and to investigate the association between travel time to hospital and
age at treatment, adjusted for medical and socioeconomic background.
Patients and Methods

Study design and study population

This was a total population study of retrospective longitudinal register data. All boys born in Sweden between January 1, 2001 until December 31, 2014 were eligible for inclusion. Study subjects were followed in national healthcare and administrative registers from birth, and they contributed until December 31 2014 unless censored due to migration, death, or outcome. Excluded were children with comorbidities that were likely to influence the standard or timing of surgical treatment (as determined by the EUROCAT list of minor malformations, n=607).[26]

Settings

The Swedish welfare system covers all citizens, and pediatric healthcare is free of charge, with no direct out-of-pocket expenses.[27] Screening for cryptorchidism was performed at birth, and at 6 and 18 months of age, as part of the regular healthy child check-ups performed by pediatricians or general practitioners with pediatric interest. Cryptorchidism is treated with an elective surgical procedure, usually performed under general anesthesia and inguinal nerve block. According to national guidelines, children younger than 12 months should be referred to a dedicated pediatric surgery unit for safe anesthesia and surgery.[12] The median age at surgery among Swedish boys has previously been estimated to decrease from just over 6 years in 2001, to just over 3 years in 2014, and the prevalence of cryptorchidism treatment was stable throughout the study period. [4]

Primary and secondary outcomes
Primary outcome was occurrence and age at surgery for cryptorchidism, and secondary outcome was occurrence and age when diagnosis first was suspected. Date of birth was adjusted for preterm delivery by adding days up to 40 weeks pregnancy. Age at surgery was determined by the date of surgery. The International Classification of Diseases, version 10 (ICD-10) and Nordic Medico-Statistical Committee Classification of Surgical Procedures (NOMESCO-CSP) were used throughout the study period for coding of diseases and procedures.[28] Cryptorchidism was defined by any ICD-10 code Q53.0-9 and Q55.0-1 and surgery for cryptorchidism was defined by any of the procedures KFH00, KFH10, JAH01, KFC00, KFC96 or KFD00 added to the ICD-code.

Exposure, risk factors and socioeconomic determinants

Primary exposure was travel time to treating hospital. The most time-efficient way from the population centroid (age 0-18 years) of each patient’s area of residence (Small Area of Market Studies, SAMS) at the time of birth to the geo-coordinates of the treating hospital was estimated, considering speed limitations, stop signals, left turns and right turns as they were at the year of birth, and reported in minutes as a continuous variable. Medical risk factors were length of pregnancy (<32 weeks, 32-36 weeks, 37-41 weeks, >42 weeks), birth weight (<1000g, 1000-1499g, 1500-2499g, 2500-4200g, >4200g), size for gestational age (small, average or large for gestational age), maternal age and smoking status during pregnancy (no smoking, 1-9 cigarettes/day or >9/day). Socioeconomic determinants included educational level of parents, unemployment, income, social transfers, and place of birth. The highest achieved education within the family was categorized either as the completion of compulsory school (<10 years), high school (<13 years) or higher education (>12
years). Unemployment was defined as any parent being registered in the Swedish Unemployment Service one year prior to inclusion. Income was determined by the sum of the parents’ income after taxations and transfers the year prior to inclusion, to avoid influence of parental leave on income, and families were categorized in annual income quintiles to adjust for inflation and shifts in taxation and regulations. Social transfers included any governmental financial support the year prior to inclusion. Parents were categorized as being born either in Sweden or elsewhere, and the child could have two, one, or no Swedish-born parents.

Data sources and data validity

The study population was identified in the Swedish Medical Birth Register (MBR).[29] Birth characteristics were collected from the MBR, and medical records were retrieved from the Swedish National Patient Register (NPR). MBR covers all births in Sweden and NPR covers >99% of inpatient care and 80-86% of specialized outpatient care including day surgery in private and public hospitals during the study period.[30,31] The Swedish Multi-Generation Register was used to identify parents in the cohort, and socioeconomic information and parental place of residence were retrieved from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA).[32,33] The Register of the Total Population (Statistics Sweden) provided information on parents’ migration status.[34] Annual data on the Swedish roads and infrastructure were collected from the Sweden’s National Road Database.[35]

Statistical analysis
Descriptive statistics presents the cohort's independent variables as distributed by levels of primary exposure. The cumulative incidence and timing of cryptorchidism diagnosis and treatment were reported as percentages and presented in Kaplan-Meier curves and assessed by log-rank test. P-values obtained by F-tests assessed the overall contribution of each categorical variable included in the regression models. Hazard ratios (HR) of each risk factor, adjusted for study year and socioeconomic determinants, were obtained by Cox regression and reported with 95% confidence intervals (CI). As primary exposure was applicable only for subjects with surgical treatment, a Cox regression model was designed to assess for treatment delay in the sub-cohort of treated children, with adjustment for year of birth, risk factors and socioeconomic determinants. Time of censoring was set to 3 years of age; an age cut-off chosen as cases of congenital cryptorchidism should have been identified and treated and acquired cryptorchidism should still have limited influence. To assess robustness of results, alternative censoring at 2 and 5 years of age was applied as well. Similarly, travel time was also categorized and included in the model on the nominal scale as a sensitivity analysis of main associations. All multivariable cox regression models were stratified on healthcare region of residence, in order to adjust for clustered data.

Software

ArcGis® 10.2, Environmental Systems Research Institute (ESRI) of Redlands, California was used to calculate travel times and STATA/SE® 14.1 for Windows was used for statistics.[36]
Results

Cumulative incidence and timing surgery

Of 748,678 boys, 7351 were treated for cryptorchidism and evaluated for timing of surgery (Figure 1). The cumulative incidence of surgically treated cryptorchidism in the oldest birth cohort (2001-2002, followed until 14 years age) was 1.4% (95% CI 1.3-1.5%). The estimated travel time from place of residence to treating hospital was 36 minutes in mean (standard deviation 58 minutes) and 20 minutes in median (IQR 11-38 minutes). More children traveled longer to the treatment later in the study period (eTable 1), and there was also a trend towards earlier diagnosis and treatment later in the study period, in particular after the introduction of national guidelines in 2007 (p<0.001, Figure 2A and eFigure 1).

Risk factors for cryptorchidism

Prematurity and overdue pregnancy were associated with increased incidence of disease (p<0.001, Figure 2B), as were low birth weight (p<0.001, Figure 2C) and intrauterine growth restriction (p<0.001, Figure 2D). Maternal age and smoking status were not associated with the incidence (p=0.42 and p=0.19). These results were robust in bivariate models with adjustment for year of birth (eFigure 2), and in a multivariable model with adjustment for socioeconomic confounders (Figure 3).

Association between travel distance and timing of treatment

The unadjusted association between travel distance and timing of treatment is presented in eFigure 3. Bivariate associational estimates of travel time and of each socioeconomic variable, with adjustment for year of birth only, are presented in eFigure 4. In the multivariable analysis, the probability of timely surgery decreased
by each 30-minute increase in travel time (adjusted HR 0.91 (95% CI 0.88-0.95), p<0.001; Figure 4). Whereas high income (p=0.001) and absence of social security support (adjusted HR 0.85 (95% CI 0.73-0.97), p=0.02) were associated with increased rate of surgical treatment before age of 3 years, no such associations were seen by levels of education, employment, or parental migration status (Figure 4). The association between travel distance to hospital and treatment age did not change substantially in any of the performed sensitivity analyses (Appendix page 7-8, eFigure 5-6).

Discussion

In this national birth-cohort study of all Swedish-born boys, cumulative incidences of cryptorchidism were determined for established risk factors of disease. The incidence by 14 years of age was 1.4%. Travel distance to the treating hospital was associated with treatment delay, also when medical and socioeconomic factors were adjusted for.

These results underline the considerable national public health implications of screening and treating cryptorchidism in boys, and confirm a remarkable increase in risk for boys born prematurely, with low birth weight or with diverging size for gestational age. The association between travel time and delayed treatment may appear counter-intuitive for a non-emergent condition like cryptorchidism. It is possible, however, that some parents could hesitate to accept a long-distance referral with their infant child, or that the result reflects a guideline-awareness gradient within the healthcare system. Regardless, the association delineates a trade-off between centralization benefits and geographical access in elective surgery for children.
Meanwhile surgical care in general, and pediatric surgery in particular, is increasingly centralized, these findings address potential problems with this transition.

The incidences and risk stratification by medical birth determinants reported here are in line with previous studies.[1–6,16,17] The biphasic pattern of the cumulative incidence seen in figure 2A indicate a second incidence peak in early school-age, presumably representing a mix of acquired cryptorchidism and late detected congenital cases. This finding is in line with earlier observations, even if reliable differentiation between acquired and late detected congenital cryptorchidism is not possible from these data.[4,23] However, maternal smoking during pregnancy did not add to the risk in our analysis, and the recently reported association of smoking on cryptorchidism risk may have been mediated by imbalances in established birth-related risk factors.[19] Whereas a few earlier studies have reported associations between rural area of residence and treatment delays in cryptorchidism[2,20,23], and one study has indicated that the general risk of increasing waiting-times for pediatric surgery for patients living further from hospital[37], this is the first study to investigate associations with the patient’s estimated travel time to elective care with adjustment for individual-level socioeconomic determinants. Interestingly, increasing travel distance was not associated with adverse outcome in pediatric appendicitis, which may reflect the generally shorter distances to emergency hospitals.[38] A few studies of cryptorchidism, in various healthcare systems and populations, have reported treatment delays for children with worse insurance status or lower average income and education in neighborhood area of residence.[2,21] This effect seems context-specific, as indicated by a Canadian study showing that average deprivation status and income level in area of residence did not associate with treatment delays in
pediatric surgery in general.[37] When multiple individual-level social determinants of health are adjusted for, the impact of income on the probability to be treated timely seems valid also in Sweden. Overall, however, socioeconomic background seems to be a relative week predictor of treatment delay in Sweden.

Limitations

This study was based on individual-level healthcare data and administrative records of a national population of children with free access to care. Consequently, the risk for selection bias due to a diversified healthcare system or financial barriers was reduced to a minimum. However, residual selection bias due to referral propensity based on age cannot be ruled out. Further, distinction between congenital and acquired cryptorchidism could not be done, which relates to the interpretation of the cumulative incidence. Due to the study design, causality cannot be claimed. In addition, associations could be susceptible to unmeasured confounding, and to uncaptured non-linear trends due to the categorization of variables. The accuracy of the administrative registers is expected to be high, yet it is possible that a hidden skewness exists, and most likely such effect would dilute the observed effects. The data sources could not provide adequate data on referral times and waiting times for surgery, and even if date of surgery is considered a reliable outcome measure of treatment delay, deeper understanding of this concept would require a more detailed analysis of the chain of care between screening and surgery. A strength of this study is that travel time to the treating hospital was measured continuously for each treated individual in this cohort. Travel time may be a more realistic measure of geographic access than measures of distance. Yet these are estimates, not exact travel times, as the trip originated at the population centroid of the area of residence rather than the
exact home address. Further, a bias may have been introduced in these calculations as
all families were expected to have access to a motor vehicle for transportation, even if
this might have varied between socioeconomic strata.

Conclusion

This study confirms that the cryptorchidism incidence among boys is tightly linked to
prematurity, low birth weight, and size for gestational age. It is the first study to
measure the association between travel time to hospital and access to timely treatment
for elective surgery in children, with adjustment for socioeconomic determinants on
individual level. We conclude that increased travel time was associated with delayed
treatment.

Ethical considerations and reporting statement

Approval to access healthcare data of the cohort was obtained from the Ethical
Review Board in Lund (2014/791 and 2015/429) and ethical approval to access
individual level socioeconomic and geographic determinants on parents was obtained
from the Central Ethical Review Board in Stockholm (Ö 19-2015), and by ethical
vetting at Statistics Sweden. The study was reported in compliance with the STROBE
guidelines.[39] It was not possible or appropriate to involve patients and public in the
research process.

Author contribution statement:

Dr. Omling and Dr. Hagander planned, designed and conceptualized the study,
applied for ethical approval, acquisitioned data, performed statistical analyses,
interpreted results, drafted and approved the manuscript.
Professor Björk planned, designed and conceptualized the study, applied for ethical approval, performed statistical analyses, interpreted results, and approved the final manuscript.

Dr. Bergbrant planned, designed and conceptualized the study, applied for ethical approval, acquisitioned data, interpreted results, and approved the final manuscript.

Associate professor Persson conceptualized the study, performed geographic data analysis, interpreted results and approved the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**Conflict of interest statement**

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Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Data sharing

Data is not available for public access. Please contact the corresponding author with requests regarding data access.
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Figure legends:

Figure 1. Inclusion and exclusion of Swedish children diagnosed and treated for cryptorchidism.

Figure 2. Cumulative incidence of surgery for cryptorchidism among 748,678 Swedish boys, by year of birth and risk factors. Follow-up was until end of 2014. Note different scales on vertical axis in Figures A and B-D. A. Age at treatment for 2-year birth cohorts. There was a shift towards earlier treatment after the introduction of Nordic guidelines in 2007. Note the biphasic shape of the curve, indicating an early peak incidence, and a second incidence peak in early school-age. B. By birth week. C. By birth weight. D. By size for gestational age.

Figure 3. Childhood incidence (age 0-14 years) and hazard ratios of surgery for cryptorchidism, by medical risk factors. Effect estimates from multivariable Cox regression model adjusted for year of birth, and socioeconomic determinants including highest education, unemployment, income, financial support and number of parents born in Sweden.

Figure 4. Hazard ratio of having had surgery at 3 years of age among boys treated for cryptorchidism, by travel time to treating hospital and socioeconomic determinants. Multivariable Cox regression model adjusted for year of birth and medical risk factors (birth week, size for gestational age, maternal smoking and age).
Exposure: Birth-related risk factors

748,678 boys born in Sweden 2001-2014

Diagnosed with cryptorchidism N = 12,239

Excluded
No surgery (n = 4260)
Comorbidity (n = 607)
Migration (n = 21)

Exposure: Travel time socioeconomic determinants

Final study population N = 7351

Primary outcome: age at surgery
By 2-year birth cohorts

By length of pregnancy

By birth weight

By size for gestational age
| Length of pregnancy (week) | Incidence n (%) | Relative Incidence Lower | Hazard ratio (95% confidence interval) | P-value |
|---------------------------|-----------------|--------------------------|---------------------------------------|---------|
| <32                       | 182 (2.6)       | 2.36 (1.97 to 2.82)      | <0.001                                |         |
| 32-36                     | 494 (1.3)       | 1.32 (1.20 to 1.46)      | 1                                     |         |
| 37-41^                    | 6021 (0.9)      | 1.18 (1.09 to 1.29)      | 1                                     |         |

| Size for gestational age  | Incidence n (%) | Relative Incidence Lower | Hazard ratio (95% confidence interval) | P-value |
|---------------------------|-----------------|--------------------------|---------------------------------------|---------|
| Small                     | 355 (2.2)       | 2.10 (1.87 to 2.37)      | <0.001                                |         |
| Average^                  | 6684 (1.0)      | 1.34 (1.19 to 1.51)      |                                      |         |
| Large                     | 312 (1.2)       | 1.34 (1.19 to 1.51)      |                                      |         |

| Maternal smoking during pregnancy | Incidence n (%) | Relative Incidence Lower | Hazard ratio (95% confidence interval) | P-value |
|-----------------------------------|-----------------|--------------------------|---------------------------------------|---------|
| No smoking^                       | 6142 (1.0)      | 1.10 (0.99 to 1.22)      | 1                                     | 0.14    |
| 1-9 cigarettes per day            | 471 (1.1)       | 1.07 (0.92 to 1.26)      |                                      |         |

| Maternal age at birth (years)     | Incidence n (%) | Relative Incidence Lower | Hazard ratio (95% confidence interval) | P-value |
|-----------------------------------|-----------------|--------------------------|---------------------------------------|---------|
| <20                               | 130 (1.1)       | 1.08 (0.86 to 1.36)      |                                      | 0.61    |
| 20-24                             | 971 (1.0)       | 0.97 (0.88 to 1.05)      |                                      |         |
| 25-29                             | 2149 (1.0)      | 0.97 (0.91 to 1.03)      |                                      |         |
| 30-34^                            | 2575 (1.0)      | 1.07 (0.92 to 1.26)      |                                      |         |
| 35-39                             | 1291 (1.0)      | 0.99 (0.92 to 1.06)      |                                      |         |
| >39                               | 235 (0.9)       | 0.90 (0.78 to 1.04)      |                                      |         |

^ Reference category chosen as baseline in the regression analysis.
| Treated for cryptorchidism at age 3 years | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|------------------------------------------|--------------------|---------------------------------------|---------|
|                                          | Later              | Earlier                               |         |
| Travel time to treating hospital         |                    |                                       |         |
| By each 30-minute increase               |                    | 0.91 (0.88 to 0.95)                   | <0.001  |
| Education (years)                        |                    |                                       |         |
| >12†                                     |                    | 1                                     | 0.64    |
| 10-12                                    |                    | 0.97 (0.90 to 1.04)                   |         |
| <10                                      |                    | 0.99 (0.82 to 1.20)                   |         |
| Employment                               |                    |                                       |         |
| Yes†                                     |                    | 1                                     | 0.19    |
| Unemployment                             |                    | 0.93 (0.84 to 1.03)                   |         |
| Income (quintiles)                       |                    |                                       | <0.001  |
| Q5, highest income†                     |                    | 1                                     |         |
| Q4                                       |                    | 0.88 (0.79 to 0.97)                   |         |
| Q3                                       |                    | 0.80 (0.72 to 0.89)                   |         |
| Q2                                       |                    | 0.90 (0.81 to 1.00)                   |         |
| Q1, lowest income                        |                    | 0.82 (0.72 to 0.93)                   |         |
| Financial support                        |                    |                                       | 0.02    |
| No support                               |                    | 1                                     |         |
| Support                                  |                    | 0.85 (0.73 to 0.97)                   |         |
| Parents born in Sweden                   |                    |                                       | 0.46    |
| Two†                                     |                    | 1                                     |         |
| One                                      |                    | 1.06 (0.96 to 1.17)                   |         |
| None                                     |                    | 1.04 (0.93 to 1.16)                   |         |

† Reference category chosen as baseline in the regression analysis.
Online-only supplement

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Table 1. Swedish-born boys treated for cryptorchidism (2001-2014), by risk factors and socioeconomic determinants (left) and travel time to treating hospital (right).

| Boys at risk | Cryptorchidism Surgery, n (%) | <30 | 30-59 | 60-89 | ≥90 |
|--------------|-------------------------------|-----|------|-------|-----|
| Total        | 748,678                       | 7351| 5006 | 1367  | 387 | 579 |

**Year of birth**

| Year          | Total | <30 (7.3) | 30-59 (12.0) | 60-89 (17.3) | ≥90 (22.0) |
|---------------|-------|-----------|--------------|--------------|------------|
| 2001-2002     | 93,895| 865 (17.3)| 247 (18.1)   | 65 (16.8)    | 91 (15.7)  |
| 2003-2004     | 100,891| 919 (18.4)| 273 (20.0)   | 71 (18.4)    | 79 (13.6)  |
| 2005-2006     | 103,839| 830 (16.6)| 201 (14.7)   | 57 (14.7)    | 80 (13.8)  |
| 2007-2008     | 108,568| 888 (17.7)| 240 (17.6)   | 68 (17.6)    | 96 (16.6)  |
| 2009-2010     | 113,669| 717 (14.3)| 220 (16.1)   | 57 (14.7)    | 102 (17.6) |
| 2011-2012     | 112,712| 629 (12.6)| 147 (10.8)   | 58 (15.0)    | 108 (18.7) |
| 2013-2014     | 115,104| 158 (3.2) | 39 (2.9)     | 11 (2.8)     | 23 (4.0)   |

**Birth weight, g**

| <1000 | 2264 (0.3) | 79 (1.1) | 46 (0.9) | 8 (0.6) | 6 (1.6) |
| >1000 | 3294 (0.4) | 112 (1.5) | 84 (1.7) | 13 (0.9) | 4 (1.0) |

**Length of pregnancy, w**

| <32     | 7121 (1.0) | 192 (2.5) | 119 (2.4) | 22 (1.6) | 12 (3.1) |
| 32-36   | 38,649 (5.2) | 494 (6.7) | 338 (6.8) | 100 (7.3) | 28 (7.2) |
| 37-41   | 644,795 (86.1) | 6021 (81.9) | 4102 (81.9) | 1130 (82.7) | 312 (80.6) |
| 42-     | 57,798 (7.7) | 646 (8.8) | 442 (8.8) | 113 (8.3) | 35 (9.0) |

**Mother age, year**

| <20 | 11,779 (1.6) | 130 (1.8) | 75 (1.5) | 29 (2.1) | 8 (2.0) |
| 20-24 | 94,900 (12.7) | 971 (13.2) | 602 (12.0) | 214 (15.7) | 62 (16.0) |
| 25-29 | 222,375 (29.7) | 2149 (29.2) | 1394 (27.9) | 429 (31.4) | 130 (33.6) |
| 30-34 | 261,366 (34.9) | 2575 (35.0) | 1818 (36.3) | 438 (32.0) | 132 (34.1) |
| 35-39 | 131,080 (17.5) | 1291 (17.6) | 944 (18.9) | 221 (16.2) | 45 (11.6) |
| >39   | 27,174 (3.6) | 235 (3.2) | 173 (3.5) | 36 (2.6) | 10 (2.6) |
| missing | 4 | - | - | - | - |

**Mother smoking**

| No | 642,436 (85.8) | 6142 (83.5) | 4207 (84.0) | 1126 (82.4) | 310 (80.1) |
| 1-9 cigarettes/d | 42,618 (5.7) | 471 (6.4) | 297 (5.9) | 109 (8.0) | 33 (8.5) |
| >9 cigarettes/d | 16,562 (2.2) | 188 (2.6) | 103 (2.1) | 50 (3.7) | 17 (4.4) |

**Parents’ education**

| >12 years | 413,452 (55.2) | 3842 (52.3) | 2814 (56.2) | 585 (42.8) | 167 (43.2) |
| 10-12 years | 270,838 (36.2) | 2863 (38.9) | 1738 (34.7) | 678 (49.6) | 188 (48.6) |
| <10 years | 26,082 (3.5) | 279 (3.8) | 183 (3.7) | 56 (4.1) | 15 (3.9) |

**Unemployed parents**

| No | 624,497 (83.4) | 6179 (84.1) | 4221 (84.3) | 1167 (85.4) | 324 (83.7) |
| Yes | 98,932 (13.2) | 934 (12.7) | 599 (12.0) | 178 (13.0) | 51 (13.2) |

**Income, quintile**

| Q5 (highest income) | 133,171 (17.8) | 1457 (19.8) | 1135 (22.7) | 189 (13.8) | 55 (14.2) |
| Q4 | 133,173 (17.8) | 1354 (18.4) | 972 (19.4) | 297 (21.7) | 70 (18.1) |
| Q3 | 133,167 (17.8) | 1399 (19.0) | 896 (17.9) | 264 (19.3) | 95 (24.6) |
| Q2 | 133,162 (17.8) | 1421 (19.3) | 811 (16.2) | 300 (22.0) | 80 (20.7) |
Figure 1. Cumulative incidence of cryptorchidism (diagnosis) among 748,678 Swedish boys, by two-year birth cohorts (2001-2014). Follow-up is until end of 2014.

Q1 (lowest income) 133,159 (17.8) 1440 (19.6) 976 (19.5) 298 (21.1) 73 (18.9) 116 (20.0)
Missing data 82,846 (11.1) 280 (3.8) 216 (4.3) 28 (2.1) 14 (3.6) 20 (3.5)

Financial support
No 657,465 (87.8) 6381 (86.8) 4321 (86.3) 1218 (89.1) 333 (86.0) 503 (86.9)
Any 69,700 (9.3) 779 (10.6) 533 (10.7) 135 (9.9) 44 (11.4) 62 (10.7)
Missing data 21,806 (2.9) 191 (2.6) 152 (3.0) 14 (1.0) 10 (2.6) 14 (2.4)

Parents born in Sweden
Two 531,191 (70.9) 5063 (68.9) 3259 (65.1) 1059 (77.5) 294 (76.0) 445 (76.9)
One 101,945 (13.6) 962 (13.1) 712 (14.2) 146 (10.7) 43 (11.1) 60 (10.4)
None 115,481 (15.4) 1324 (18.0) 1035 (20.7) 161 (11.8) 50 (12.9) 74 (12.8)
Missing data 61 (0.0) 2 (0.0) - 1 (0.1) - -

* 12 subjects with missing on travel time.
| Cryptorchidism treatment | Yes n (%) | Relative incidence | Hazard ratio (95% confidence interval) | P-value |
|-------------------------|-----------|--------------------|----------------------------------------|---------|
| Birth weight (gram)     |           |                    |                                       | <0.001  |
| ELBWa (<1000 gram)      | 79 (3.5)  |                    | 3.94 (3.15 to 4.92)                  |         |
| VLBVb (1000-1499 gram)  | 112 (3.4) |                    | 3.70 (3.07 to 4.46)                  |         |
| LBWc (1500-2499 gram)   | 372 (1.6) |                    | 1.69 (1.52 to 1.88)                  |         |
| Normal (2500-4199 gram) | 5796 (0.9)|                    | 1                                     |         |
| Heavy (≥ 4200 gram)     | 970 (1.0) |                    | 1.06 (0.99 to 1.13)                  |         |
| Size for gestational age|           |                    |                                       | <0.001  |
| Small (SGA)             | 355 (2.2) |                    | 2.38 (2.14 to 2.65)                  |         |
| Average (AGA) ref       | 6684 (0.9)|                    | 1                                     |         |
| Large (LGA)             | 312 (1.2) |                    | 1.26 (1.13 to 1.42)                  |         |
| Length of pregnancy     |           |                    |                                       | <0.001  |
| <32 weeks               | 182 (2.6) |                    | 2.77 (2.39 to 3.21)                  |         |
| 32-36 weeks             | 494 (1.3) |                    | 1.36 (1.24 to 1.49)                  |         |
| 37-41 weeks ref         | 6021 (0.9)|                    | 1                                     |         |
| >42 weeks               | 646 (1.1) |                    | 1.19 (1.10 to 1.29)                  |         |
| Maternal smoking        |           |                    |                                       | 0.13    |
| No smoking (ref)        | 6142 (1.0)|                    | 1                                     |         |
| 1-9 cigarettes/d        | 471 (1.1) |                    | 1.09 (0.99 to 1.19)                  |         |
| >9 cigarettes/d         | 6801 (1.0)|                    | 1.08 (0.93 to 1.25)                  |         |
| Age of mother (years)   |           |                    |                                       | 0.35    |
| <20                     | 130 (1.1) |                    | 1.08 (0.91 to 1.29)                  |         |
| 20-24                   | 971 (1.0) |                    | 1.05 (0.98 to 1.14)                  |         |
| 25-29                   | 2149 (1.0)|                    | 0.99 (0.93 to 1.04)                  |         |
| 30-34 (ref)             | 2575 (1.0)|                    | 1                                     |         |
| 35-39                   | 1291 (1.0)|                    | 1.02 (0.95 to 1.09)                  |         |
| >39                     | 235 (0.9) |                    | 0.92 (0.81 to 1.06)                  |         |
| Education (years)       |           |                    |                                       | 0.002   |
| >12 (ref)               | 3842 (0.9)|                    | 1                                     |         |
| 10-12                   | 2863 (1.1)|                    | 1.08 (1.02 to 1.13)                  |         |
| <10                     | 279 (1.1) |                    | 1.15 (1.02 to 1.30)                  |         |
| Employment              |           |                    |                                       | 0.53    |
| Yes (ref)               | 6179 (1.0)|                    | 1                                     |         |
| Unemployment            | 934 (0.9) |                    | 1.02 (0.95 to 1.10)                  |         |
| Income (quintiles)      |           |                    |                                       | 0.15    |
| Q5, highest income (ref)| 1440 (1.1)|                    | 1                                     |         |
| Q4                      | 1421 (1.1)|                    | 0.98 (0.91 to 1.05)                  |         |
| Q3                      | 1399 (1.1)|                    | 0.96 (0.90 to 1.04)                  |         |
| Q2                      | 1354 (1.0)|                    | 0.93 (0.87 to 1.01)                  |         |
| Q1, lowest income       | 1457 (1.1)|                    | 1.02 (0.95 to 1.10)                  |         |
| Financial support       |           |                    |                                       | <0.001  |
| No support (ref)        | 6381 (1.0)|                    | 1                                     |         |
| Support                 | 779 (1.1) |                    | 1.15 (1.07 to 1.24)                  |         |
| Parents born in Sweden  |           |                    |                                       | <0.001  |
| Two (ref)               | 5063 (1.0)|                    | 1                                     |         |
| One                     | 962 (0.9) |                    | 1.06 (0.99 to 1.14)                  |         |
| None                    | 1324 (1.1)|                    | 1.37 (1.29 to 1.46)                  |         |

eFigure 2. Childhood Incidence of cryptorchidism, hazard ratio by risk factors and socioeconomic variables. Bivariate logistic models, adjusted for year of birth.
eFigure 3. Timing of surgery among children treated for cryptorchidism. The cumulative proportion, by non-adjusted levels of travel time to hospital. Children born in Sweden 2001-2014, followed until 5 years of age.
| Travel time to treating hospital (minutes) | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|-------------------------------------------|---------------------|----------------------------------------|---------|
| By each 30-minutes increase               |                     | 0.91 (0.88 to 0.95)                    | <0.001  |
| By categories                             |                     |                                        |         |
| <30 (ref)                                 |                     | 1                                      |         |
| 30-59                                     |                     | 0.84 (0.77 to 0.91)                    |         |
| 60-89                                     |                     | 0.72 (0.62 to 0.82)                    |         |
| >90                                       |                     | 0.84 (0.76 to 0.94)                    |         |
| **Education (years)**                     |                     |                                        | 0.001   |
| >12 (ref)                                 |                     | 1                                      |         |
| 10-12                                     |                     | 0.90 (0.84 to 0.96)                    |         |
| <10                                       |                     | 0.82 (0.70 to 0.97)                    |         |
| **Full employment**                       |                     |                                        | 0.003   |
| Yes (ref)                                 |                     | 1                                      |         |
| No                                        |                     | 0.87 (0.80 to 0.95)                    |         |
| **Income (quintiles)**                    |                     |                                        | <0.001  |
| Q5, highest income (ref)                  |                     | 1                                      |         |
| Q4                                        |                     | 0.87 (0.79 to 0.95)                    |         |
| Q3                                        |                     | 0.79 (0.72 to 0.87)                    |         |
| Q2                                        |                     | 0.86 (0.78 to 0.95)                    |         |
| Q1, lowest income                         |                     | 0.76 (0.69 to 0.84)                    |         |
| **Financial support**                     |                     |                                        | <0.001  |
| No support (ref)                          |                     | 1                                      |         |
| Support                                   |                     | 0.81 (0.73 to 0.90)                    |         |
| **Parents born in Sweden**                |                     |                                        | 0.15    |
| Two (ref)                                 |                     | 1                                      |         |
| One                                       |                     | 1.07 (0.98 to 1.17)                    |         |
| None                                      |                     | 0.96 (0.89 to 1.04)                    |         |

**Figure 4.** Relative incidence of treatment for cryptorchidism before 3 years of age, and hazard ratio by travel time to treating hospital and socioeconomic determinants. Bivariate Cox regression model adjusted for year of birth, without adjustment for risk factors.
Sensitivity analysis of main associations

The estimated hazard ratio for treatment by levels of travel time did not change substantially when travel time was presented as categories on the nominal scale (<30 minutes travel time being reference, the adjusted HR for 30-59 minutes travel time: 0.82 [95% CI 0.75 to 0.90]; adjusted HR for 60-89 minutes: 0.72 [95% CI 0.62 to 0.83]; and adjusted HR for 90 minutes or more: 0.84 [95% CI 0.74 to 0.95], p<0.001 for overall variable contribution). Later in the study period, more children had a longer travel time to hospital (eTable 1). Robustness of the results by the introduction of Nordic guidelines in 2007 were therefore tested by splitting the cohort in two, based on year of birth (2001-2006 and 2007-2014). This resulted in similar hazard ratios (by each 30-minute increase in travel time for children born 2001-2006; adjusted HR 0.90 [95% CI 0.83 to 0.96], p=0.003, and for children born 2007-2014; adjusted HR 0.92 [95% CI 0.88 to 0.96], p<0.001). The main association was also robust to changes in age cut-off in the survival analysis (eFigures 5 and 6). In fact, the relative incidence of being treated was even higher at age 2 years (treatment rate by each 30-minute increase in travel time: adjusted HR 0.87 [95% CI 0.83 to 0.91], p<0.001) and remained at age 5 years (adjusted HR 0.96 [95% CI 0.92 to 1.00], p=0.03).

### Treated for cryptorchidism at age 2

| Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|---------------------|---------------------------------------|---------|
| Later               | 0.87 (0.83 to 0.91)                   | <0.001  |
| Earlier             |                                       |         |

### Education (years)

| Level     | Hazard ratio (95% confidence interval) | P-value |
|-----------|---------------------------------------|---------|
| >12 (ref) |                                       |         |
| 10-12     | 0.95 (0.87 to 1.03)                   |         |
| <10       | 0.96 (0.77 to 1.21)                   |         |

### Employment

| Status     | Hazard ratio (95% confidence interval) | P-value |
|------------|---------------------------------------|---------|
| Yes (ref)  |                                       |         |
| Unemployment| 0.92 (0.81 to 1.04)                   |         |

### Income (quintiles)

| Quintile       | Hazard ratio (95% confidence interval) | P-value |
|----------------|---------------------------------------|---------|
| Q5, highest income (ref) |                                       |         |
| Q4              | 0.84 (0.74 to 0.94)                   |         |
| Q3              | 0.72 (0.64 to 0.82)                   |         |
| Q2              | 0.85 (0.75 to 0.96)                   |         |
| Q1, lowest income | 0.78 (0.67 to 0.91)                  | <0.001  |

### Financial support

| Support Status | Hazard ratio (95% confidence interval) | P-value |
|---------------|---------------------------------------|---------|
| No support (ref) |                                       |         |
| Support        | 0.81 (0.68 to 0.97)                   | 0.02    |

### Parents born in Sweden

| Status       | Hazard ratio (95% confidence interval) | P-value |
|--------------|---------------------------------------|---------|
| Two (ref)    |                                       |         |
| One          | 1.05 (0.93 to 1.18)                   | 0.64    |
| None         | 1.05 (0.92 to 1.19)                   |         |

### eFigure 5. Sensitivity analysis

**Hazard ratio of treatment for cryptorchidism before 2 years of age, by travel time to treating hospital and socioeconomic determinants.** Multivariable Cox regression model adjusted for year of birth and risk factors (birth week, size for gestational age, maternal smoking and age). Children born 2001-2014, followed 24 months from birth.
| Travel time to hospital (minutes) | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|----------------------------------|---------------------|----------------------------------------|---------|
| By each 30-minute increase       | Later               | 0.95 (0.92 to 0.98)                     | 0.001   |
| **Education** (years)            |                     |                                        |         |
| >12 (ref)                        | Earlier             | 1                                      | 0.80    |
| 10-12                            |                     | 0.99 (0.93 to 1.06)                     |         |
| <10                              |                     | 0.95 (0.80 to 1.12)                     |         |
| **Employment**                   |                     |                                        | 0.20    |
| Yes (ref)                        |                     | 1                                      |         |
| Unemployment                     |                     | 0.94 (0.86 to 1.03)                     |         |
| **Income** (quintiles)           |                     |                                        | 0.003   |
| Q5, highest income group (ref)   |                     | 1                                      |         |
| Q4                               |                     | 0.90 (0.83 to 0.99)                     |         |
| Q3                               |                     | 0.83 (0.75 to 0.91)                     |         |
| Q2                               |                     | 0.89 (0.80 to 0.98)                     |         |
| Q1, lowest income                |                     | 0.88 (0.78 to 0.98)                     |         |
| **Financial support**            |                     |                                        | 0.005   |
| No support (ref)                 |                     | 1                                      |         |
| Support                          |                     | 0.84 (0.74 to 0.95)                     |         |
| **Parents born in Sweden**       |                     |                                        | 0.63    |
| Two (ref)                        |                     | 1                                      |         |
| One                              |                     | 1.04 (0.95 to 1.14)                     |         |
| None                             |                     | 1.03 (0.94 to 1.14)                     |         |

**eFigure 6.** Sensitivity analysis. Hazard ratio of treatment for cryptorchidism before 5 years of age, by travel time to treating hospital and socioeconomic determinants. Multivariable Cox regression model adjusted for year of birth and risk factors (birth week, size for gestational age, maternal smoking and age). Children born 2001-2014, followed 60 months from birth.
How boys and testicles wander to surgery: a nationwide cohort study of surgical delay in Sweden

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How boys and testicles wander to surgery:
a nationwide cohort study of surgical delay in Sweden

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Abbreviations: MBR: Swedish Medical Birth Register. SAMS: Small Area of Market Studies. NPR: National Patient Register. SGA: small for gestational age, AGA: average for gestational age, LGA: large for gestational age. G: grams. HR: hazard ratio. CI: confidence interval.

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Abstract

Background: Early orchidopexy is recommended for cryptorchidism and the surgery is increasingly centralized. The objectives were to determine the incidence, risk factors, and if distance to treating hospital impacted on timely treatment of cryptorchidism.

Methods: In this observational study, all boys born in Sweden 2001-2014 were followed in national registers to determine the incidence of cryptorchidism by levels of birth-related risk factors and social determinants. Travel time to hospital was used as the primary exposure in multivariable survival analysis, with age at surgery as main outcome.

Results: Of 748,678 boys at risk for cryptorchidism, 7351 were treated and evaluated for timing of surgery (cumulative childhood incidence 1.4%, 95% CI 1.3-1.5%). The incidence was clearly associated with prematurity and overdue pregnancy (hazard ratio for <32 weeks 2.77 [95% CI 2.39-3.21]; 32-36 weeks HR 1.36 [95% CI 1.24-1.49]; >41 weeks HR1.19 [95% CI 1.10-1.29]), low birth weight (<1000 grams HR 3.94 [95% CI 3.15-4.92]; 1000-1499 grams HR 3.70 [95% CI 3.07-4.46];1500-2500 grams HR 1.69 [95% CI 1.52-1.88]), and intrauterine growth restriction (small for gestational age HR 2.38 [95% CI 2.14-2.65]; large for gestational age HR 1.26 [95% CI 1.13-1.42]), but not with smoking or maternal age. Each 30-minute increase in travel time was associated with a reduced probability of timely treatment (hazard ratio for being treated by age 3 adjusted for risk factors and socioeconomic determinants: 0.91 [95% CI 0.88-0.95]). Lower income and financial support were also associated with treatment delays (adjusted hazard ratio for lowest income quintile 0.82 [95% CI 0.72-0.93] and for families with financial support 0.85 [95% CI 0.73-0.97]).
Conclusions: Travel distance to treating hospital was associated with delayed treatment. “Not all those who wander are lost”, but these findings suggest a trade-off between centralization benefits and barriers of geography also in elective pediatric surgery.

Key words: Cryptorchidism, incidence, risk factor, treatment delay, geography, socioeconomic

Summary box

What is known about the subject
Cryptorchidism should be treated early, preferably before 18 months of life, to avoid complications such as malignancy and infertility later in life. Risk factors for disease include prematurity and low birth weight. Pediatric anesthesia for young children is increasingly centralized to tertiary centers, while corrective surgery for older children can be performed in hospitals closer to where families live.

What this study adds
In this study, the age at surgery varied with travel time to the hospital, with less chance of timely treatment for those living further from the hospital. These results imply a trade-off between centralization benefits and geographical access to healthcare. Also, lower income and financial support were associated with treatment delays.
**Introduction**

Cryptorchidism is the most common genital anomaly in boys, with a reported prevalence of 1.0-10.7%, depending on population and risk group.[1–6] Normal testicular descent is completed in the third trimester and there is limited advancement 6 months after birth. Cryptorchid testicles are associated with impaired semen quality, reduced fertility and increased risk of testicular malignancies later in life[7–11], and for these reasons most guidelines and screening programs aim for diagnosis and treatment at 6-18 months of age.[12–15] Risk factors include preterm birth, low birth weight, and intrauterine growth restriction [1,4,5,16,17], and genetic or environmental factors may explain some differences in prevalence in various populations.[16] Recent studies have suggested that maternal smoking and obesity add to this risk, even if such studies have not considered the explanatory effect of prematurity-related risk factors on the common pathway to disease.[18,19] A few epidemiologic studies have claimed that socioeconomic background, rurality and insurance status are associated with delayed treatment. [2,20,21] However, these studies were either based on population aggregates or averages for area of residence rather than individual level data, or have not shown any clear association with the risk for delay.[22–24]

In Sweden, like many other countries, neonatal surgery and anesthesia is increasingly centralized to improve surgical outcomes for rare diseases and for the safety of anesthesia to the youngest.[25] Current guidelines for the Nordic countries recommend treatment for congenital cryptorchidism to be performed at specialized pediatric surgery departments at 6-12 months of age,[12] but only a small minority of boys with cryptorchidism are treated at that age.[4] It is unclear to what extent the centralization of pediatric surgical care has become a barrier for children with less complicated conditions living far away, and if families tend to wait until their local
hospital can help them. No study has investigated how travel time or distance to treatment impact on delay and timing of surgery for cryptorchidism.

We performed a 14-year national register-based prospective cohort study for all boys in Sweden, with inclusion of individual-level medical and socioeconomic risk factors. The aim of this total population study was to determine incidence and risk factors for cryptorchidism, and to investigate the association between travel time to hospital and age at treatment, adjusted for medical and socioeconomic background.
Patients and Methods

Study design and study population

This was a total population study of retrospective longitudinal register data. All boys born in Sweden between January 1, 2001 until December 31, 2014 were eligible for inclusion. Study subjects were followed in national healthcare and administrative registers from birth, and they contributed until December 31 2014 unless censored due to migration, death, or outcome. Excluded were children with comorbidities that were likely to influence the standard or timing of surgical treatment (as determined by the EUROCAT list of minor malformations, n=607).[26]

Settings

The Swedish welfare system covers all citizens, and pediatric healthcare is free of charge, with no direct out-of-pocket expenses.[27] Screening for cryptorchidism was performed at birth, and at 6 and 18 months of age, as part of the regular healthy child check-ups performed by pediatricians or general practitioners with pediatric interest. Cryptorchidism is treated with an elective surgical procedure, usually performed under general anesthesia and inguinal nerve block. According to national guidelines, children younger than 12 months should be referred to a dedicated pediatric surgery unit for safe anesthesia and surgery.[12] The median age at surgery among Swedish boys has previously been estimated to decrease from just over 6 years in 2001, to just over 3 years in 2014, and the prevalence of cryptorchidism treatment was stable throughout the study period. [4]

Primary and secondary outcomes
Primary outcome was occurrence and age at surgery for cryptorchidism, and secondary outcome was occurrence and age when diagnosis first was suspected. Date of birth was adjusted for preterm delivery by adding days up to 40 weeks pregnancy. Age at surgery was determined by the date of surgery. The International Classification of Diseases, version 10 (ICD-10) and Nordic Medico-Statistical Committee Classification of Surgical Procedures (NOMESCO-CSP) were used throughout the study period for coding of diseases and procedures.[28] Cryptorchidism was defined by any ICD-10 code Q53.0-9 and Q55.0-1 and surgery for cryptorchidism was defined by any of the procedures KFH00, KFH10, JAH01, KFC00, KFC96 or KFD00 added to the ICD-code.

Exposure, risk factors and socioeconomic determinants

Primary exposure was travel time to treating hospital. The most time-efficient way from the population centroid (age 0-18 years) of each patient’s area of residence (Small Area of Market Studies, SAMS) at the time of birth to the geo-coordinates of the treating hospital was estimated, considering speed limitations, stop signals, left turns and right turns as they were at the year of birth, and reported in minutes as a continuous variable. Medical risk factors were length of pregnancy (<32 weeks, 32-36 weeks, 37-41 weeks, >42 weeks), birth weight (<1000g, 1000-1499g, 1500-2499g, 2500-4200g, >4200g), size for gestational age (small, average or large for gestational age), maternal age and smoking status during pregnancy (no smoking, 1-9 cigarettes/day or >9/day). Socioeconomic determinants included educational level of parents, unemployment, income, social transfers, and place of birth. The highest achieved education within the family was categorized either as the completion of compulsory school (<10 years), high school (<13 years) or higher education (>12 years).
years). Unemployment was defined as any parent being registered in the Swedish Unemployment Service one year prior to inclusion. Income was determined by the sum of the parents’ income after taxations and transfers the year prior to inclusion, to avoid influence of parental leave on income, and families were categorized in annual income quintiles to adjust for inflation and shifts in taxation and regulations. Social transfers included any governmental financial support the year prior to inclusion. Parents were categorized as being born either in Sweden or elsewhere, and the child could have two, one, or no Swedish-born parents.

Data sources and data validity

The study population was identified in the Swedish Medical Birth Register (MBR).[29] Birth characteristics were collected from the MBR, and medical records were retrieved from the Swedish National Patient Register (NPR). MBR covers all births in Sweden and NPR covers >99% of inpatient care and 80-86% of specialized outpatient care including day surgery in private and public hospitals during the study period.[30,31] The Swedish Multi-Generation Register was used to identify parents in the cohort, and socioeconomic information and parental place of residence were retrieved from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA).[32,33] The Register of the Total Population (Statistics Sweden) provided information on parents’ migration status.[34] Annual data on the Swedish roads and infrastructure were collected from the Sweden’s National Road Database.[35]

Statistical analysis
Descriptive statistics presents the cohort's independent variables as distributed by levels of primary exposure. As we regarded the study population to be restricted in time and space, confidence intervals and p-values were reported as measures of the statistical uncertainty. The cumulative incidence and timing of cryptorchidism diagnosis and treatment were reported as percentages and presented in Kaplan-Meier curves and assessed by log-rank test. P-values obtained by F-tests assessed the overall contribution of each categorical variable included in the regression models. Hazard ratios (HR) of each risk factor, adjusted for study year and socioeconomic determinants, were obtained by Cox regression and reported with 95% confidence intervals (CI). As primary exposure was applicable only for subjects with surgical treatment, a Cox regression model was designed to assess for treatment delay in the sub-cohort of treated children, with adjustment for year of birth, risk factors and socioeconomic determinants. Time of censoring was set to 3 years of age; an age cut-off chosen as cases of congenital cryptorchidism should have been identified and treated and acquired cryptorchidism should still have limited influence. To assess robustness of results, alternative censoring at 2 and 5 years of age was applied as well. Similarly, travel time was also categorized and included in the model on the nominal scale as a sensitivity analysis of main associations. To assess sensitivity to uncaptured non-linearity in main associations of travel time, continuous variables were also analyzed with cubic splines and F-test, and the overall contribution of the variable to the model were assessed with F-test. All multivariable cox regression models were stratified on healthcare region of residence, in order to adjust for clustered data.

Software
ArcGis® 10.2, Environmental Systems Research Institute (ESRI) of Redlands, California was used to calculate travel times and STATA/SE® 14.1 for Windows was used for statistics.[36]
Results

Cumulative incidence and timing surgery

Of 748,678 boys, 7351 were treated for cryptorchidism and evaluated for timing of surgery (Figure 1). The cumulative incidence of surgically treated cryptorchidism in the oldest birth cohort (2001-2002, followed until 14 years age) was 1.4% (95% CI 1.3-1.5%). The estimated travel time from place of residence to treating hospital was 36 minutes in mean (standard deviation 58 minutes) and 20 minutes in median (IQR 11-38 minutes). More children traveled longer to the treatment later in the study period (eTable 1), and there was also a trend towards earlier diagnosis and treatment later in the study period, in particular after the introduction of national guidelines in 2007 (p<0.001, Figure 2A and eFigure 1).

Risk factors for cryptorchidism

Prematurity and overdue pregnancy were associated with increased incidence of disease (adjusted for year of birth: <32 weeks HR 2.77 [95% CI 2.39-3.21], p<0.001; 32-36 weeks HR 1.36 [95% CI 1.24-1.49], p<0.001; >41 weeks HR1.19 [95% CI 1.10-1.29], p<0.001, Figure 2B), as were low birth weight (adjusted for year of birth: <1000 grams HR 3.94 [95% CI 3.15-4.92], p<0.001; 1000-1499 grams HR 3.70 [95% CI 3.07-4.46], p<0.001; 1500-2500 grams HR 1.69 [95% CI 1.52-1.88], p<0.001; >4200 grams HR 1.05 [95% CI 0.99-1.13], p=0.12, Figure 2C) and intrauterine growth restriction (adjusted for year of birth: small for gestational age HR 2.38 [95% CI 2.14-2.65], p<0.001; large for gestational age HR 1.26 [95% CI 1.13-1.42], p<0.001, Figure 2D). Maternal age and smoking status were not associated with the incidence (log rank test p=0.42 and p=0.19 respectively). These results were robust in
bivariate models with adjustment for year of birth (eFigure 2), and in a multivariable model with adjustment for socioeconomic confounders (Figure 3).

**Association between travel distance and timing of treatment**

The unadjusted association between travel distance and timing of treatment is presented in eFigure 3. Bivariate associational estimates of travel time and of each socioeconomic variable, with adjustment for year of birth only, are presented in eFigure 4. In the multivariable analysis, the probability of timely surgery decreased by each 30-minute increase in travel time (adjusted HR 0.91 (95% CI 0.88-0.95), p<0.001; Figure 4). Whereas high income (p=0.001) and absence of social security support (adjusted HR 0.85 (95% CI 0.73-0.97), p=0.02) were associated with increased rate of surgical treatment before age of 3 years, no such associations were seen by levels of education, employment, or parental migration status (Figure 4). The association between travel distance to hospital and treatment age did not change substantially in any of the performed sensitivity analyses (Appendix page 7-9, eFigure 5-7).

**Discussion**

In this national birth-cohort study of all Swedish-born boys, cumulative incidences of cryptorchidism were determined for established risk factors of disease. The incidence by 14 years of age was 1.4%. Travel distance to the treating hospital was clearly associated with treatment delay, also when medical and socioeconomic factors were adjusted for.
These results underline the considerable national public health implications of screening and treating cryptorchidism in boys, and confirm a remarkable increase in risk for boys born prematurely, with low birth weight or with diverging size for gestational age. The association between travel time and delayed treatment may appear counter-intuitive for a non-emergent condition like cryptorchidism. It is possible, however, that some parents could hesitate to accept a long-distance referral with their infant child, or that the result reflects a guideline-awareness gradient within the healthcare system. Regardless, the association delineates a trade-off between centralization benefits and geographical access in elective surgery for children. Meanwhile surgical care in general, and pediatric surgery in particular, is increasingly centralized, these findings address potential problems with this transition.

The incidences and risk stratification by medical birth determinants reported here are in line with previous studies.[1–6,16,17] The biphasic pattern of the cumulative incidence seen in figure 2A indicate a second incidence peak in early school-age, presumably representing a mix of acquired cryptorchidism and late detected congenital cases. This finding is in line with earlier observations, even if reliable differentiation between acquired and late detected congenital cryptorchidism is not possible from these data.[4,23] However, maternal smoking during pregnancy did not add to the risk in our analysis, and the recently reported association of smoking on cryptorchidism risk may have been mediated by imbalances in established birth-related risk factors.[19]

Earlier studies have suggested associations between rural area of residence and treatment delays in cryptorchidism. However, these studies were either based on
population aggregates or averages for area of residence rather than individual level data, or have not shown any clear association with the risk for delay [2,20,22,23]. One study has reported increasing waiting-times for pediatric surgery in general among patients living further from hospital.[37] This study confirms that the patient’s travel time to elective care, when adjusted for individual-level socioeconomic determinants, do relate to timely treatment. Interestingly in this context, increasing travel distance was not associated with adverse outcome in pediatric appendicitis, which may reflect the generally shorter distances to emergency hospitals.[38] A few studies of cryptorchidism, in various healthcare systems and populations, have reported treatment delays for children with worse insurance status or lower average income and education in neighborhood area of residence.[2,21] This effect seems context-specific, as indicated by a Canadian study showing that average deprivation status and income level in area of residence did not associate with treatment delays in pediatric surgery in general.[37] In comparison, high family income do seem to increase the probability to be treated timely within the Swedish healthcare system. Overall, however, socioeconomic background seems to be a relative week predictor of treatment delay in Sweden.

Limitations

This study was based on individual-level healthcare data and administrative records of a national population of children with free access to care. Consequently, the risk for selection bias due to a diversified healthcare system or financial barriers was reduced to a minimum. However, residual selection bias due to referral propensity based on age cannot be ruled out. Further, distinction between congenital and acquired cryptorchidism could not be done, which relates to the interpretation of the
cumulative incidence. Due to the study design, causality cannot be claimed. In addition, associations could be susceptible to unmeasured confounding. However, the susceptibility to uncaptured non-linear trends due to the categorization of variables is likely low, as the main association was unchanged regardless of how continuous variables were treated in the regression model. The accuracy of the administrative registers is expected to be high, yet it is possible that a hidden skewness exists, and most likely such effect would dilute the observed effects. The data sources could not provide adequate data on referral times and waiting times for surgery, and even if date of surgery is considered a reliable outcome measure of treatment delay, deeper understanding of this concept would require a more detailed analysis of the chain of care between screening and surgery. A strength of this study is that travel time to the treating hospital was measured continuously for each treated individual in this cohort. Travel time may be a more realistic measure of geographic access than measures of distance. Yet these are estimates, not exact travel times, as the trip originated at the population centroid of the area of residence rather than the exact home address. Further, a bias may have been introduced in these calculations as all families were expected to have access to a motor vehicle for transportation, even if this might have varied between socioeconomic strata.

**Conclusion**

This study confirms that the cryptorchidism incidence among boys is tightly linked to prematurity, low birth weight, and size for gestational age. The association between travel time to hospital and access to timely treatment for elective surgery in children were measured, with adjustment for socioeconomic determinants on individual level. We conclude that increased travel time was associated with delayed treatment.
Ethical considerations and reporting statement

Approval to access healthcare data of the cohort was obtained from the Ethical Review Board in Lund (2014/791 and 2015/429) and ethical approval to access individual level socioeconomic and geographic determinants on parents was obtained from the Central Ethical Review Board in Stockholm (Ö 19-2015), and by ethical vetting at Statistics Sweden. The study was reported in compliance with the STROBE guidelines.[39] It was not possible or appropriate to involve patients and public in the research process.

Author contribution statement:

Dr. Omling and Dr. Hagander planned, designed and conceptualized the study, applied for ethical approval, acquisitioned data, performed statistical analyses, interpreted results, drafted and approved the manuscript.

Professor Björk planned, designed and conceptualized the study, applied for ethical approval, performed statistical analyses, interpreted results, and approved the final manuscript.

Dr. Bergbrant planned, designed and conceptualized the study, applied for ethical approval, acquisitioned data, interpreted results, and approved the final manuscript.

Associate professor Persson conceptualized the study, performed geographic data analysis, interpreted results and approved the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest statement
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**Transparency declaration**
The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

**Data sharing**

Data is not available for public access. Please contact the corresponding author with requests regarding data access.
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Figure legends:

Figure 1. Inclusion and exclusion of Swedish children diagnosed and treated for cryptorchidism.

Figure 2. Cumulative incidence of surgery for cryptorchidism among 748,678 Swedish boys, by year of birth and risk factors. Follow-up was until end of 2014. Note different scales on vertical axis in Figures A and B-D. A. Age at treatment for 2-year birth cohorts. There was a shift towards earlier treatment after the introduction of Nordic guidelines in 2007. Note the biphasic shape of the curve, indicating an early peak incidence, and a second incidence peak in early school-age. B. By birth week. C. By birth weight. D. By size for gestational age.

Figure 3. Childhood incidence (age 0-14 years) and hazard ratios of surgery for cryptorchidism, by medical risk factors. Effect estimates from multivariable Cox regression model adjusted for year of birth, and socioeconomic determinants including highest education, unemployment, income, financial support and number of parents born in Sweden.

Figure 4 Hazard ratio of having had surgery at 3 years of age among boys treated for cryptorchidism, by travel time to treating hospital and socioeconomic determinants. Multivariable Cox regression model adjusted for year of birth and medical risk factors (birth week, size for gestational age, maternal smoking and age).
By 2-year birth cohorts

By length of pregnancy

By birth weight

By size for gestational age

Birth week

<32

32-36

37-41

>42

Log rank test: p<0.001

Log rank test: <0.001

Log rank test: <0.001

Log rank test: <0.001

Cumulative incidence (%)

Cumulative incidence (%)

Cumulative incidence (%)

Years (years)
| Treated for cryptorchidism by age 14 | Incidence (%) | Relative incidence | Hazard ratio (95% confidence interval) | P-value |
|--------------------------------------|---------------|--------------------|----------------------------------------|---------|
|                                      | Length of pregnancy (week) |           | Lower | Higher | <0.001 |
|                                      | <32           | 182 (2.6)          | 2.36  | 1.97 to 2.82 |
|                                      | 32-36         | 494 (1.3)          | 1.32  | 1.20 to 1.46 |
|                                      | 37-41*        | 6021 (0.9)         | 1     | 1       |
|                                      | >41           | 646 (1.1)          | 1.18  | 1.09 to 1.29 |
| Size for gestational age             |               | <0.001             |        |         |
| Small                                | 355 (2.2)     | 2.10  | 1.87 to 2.37 |
| Average*                             | 6684 (1.0)    | 1     | 1       |
| Large                                | 312 (1.2)     | 1.34  | 1.19 to 1.51 |
| Maternal smoking during pregnancy    |               | 0.14              |        |         |
| No smoking*                          | 6142 (1.0)    | 1     | 1       |
| 1-9 cigarettes per day              | 471 (1.1)     | 1.10  | 0.99 to 1.22 |
| >9 cigarettes per day               | 188 (1.1)     | 1.07  | 0.92 to 1.26 |
| Maternal age at birth (years)       |               | 0.61              |        |         |
| <20                                  | 130 (1.1)     | 1.08  | 0.86 to 1.36 |
| 20-24                                | 971 (1.0)     | 0.97  | 0.88 to 1.05 |
| 25-39                                | 2149 (1.0)    | 0.97  | 0.91 to 1.03 |
| 30-34*                               | 2575 (1.0)    | 1     | 1       |
| 35-39                                | 1291 (1.0)    | 0.99  | 0.92 to 1.06 |
| >39                                  | 235 (0.9)     | 0.90  | 0.78 to 1.04 |

*Reference category chosen as baseline in the regression analysis.
| Treated for cryptorchidism at age 3 years | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|-----------------------------------------|---------------------|---------------------------------------|---------|
|                                        | Later               | Earlier                               |         |
| Travel time to treating hospital        |                     |                                       |         |
| By each 30-minute increase              |                     | 0.91 (0.88 to 0.95)                  | <0.001  |
| Education (years)                       |                     |                                       |         |
| >12                                     |                     | 1                                     | 0.64    |
| 10-12                                   |                     | 0.97 (0.90 to 1.04)                  |         |
| <10                                     |                     | 0.99 (0.82 to 1.20)                  |         |
| Employment                              |                     |                                       | 0.19    |
| Yes                                     |                     | 1                                     |         |
| Unemployment                            |                     | 0.93 (0.84 to 1.03)                  |         |
| Income (quintiles)                      |                     |                                       | <0.001  |
| Q5, highest income*                     |                     | 1                                     |         |
| Q4                                       |                     | 0.88 (0.79 to 0.97)                  |         |
| Q3                                       |                     | 0.80 (0.72 to 0.89)                  |         |
| Q2                                       |                     | 0.90 (0.81 to 1.00)                  |         |
| Q1, lowest income                       |                     | 0.82 (0.72 to 0.93)                  |         |
| Financial support                       |                     |                                       | 0.02    |
| No support                              |                     | 1                                     |         |
| Support                                 |                     | 0.85 (0.73 to 0.97)                  |         |
| Parents born in Sweden                  |                     |                                       | 0.46    |
| Two*                                    |                     | 1                                     |         |
| One                                     |                     | 1.06 (0.96 to 1.17)                  |         |
| None                                    |                     | 1.04 (0.93 to 1.16)                  |         |

* Reference category chosen as baseline in the regression analysis.
Online-only supplement

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**Table 1.** Swedish-born boys treated for cryptorchidism (2001-2014), by risk factors and socioeconomic determinants (left) and travel time to treating hospital (right).

|                     | Boys at risk n (%) | Cryptorchidism Surgery, n (%) | Travel time to treating hospital (minutes) a |
|---------------------|--------------------|--------------------------------|---------------------------------------------|
|                     | Total              |                                | 30-59                                       |
| Year of birth       |                    |                                | 60-89                                       |
| 2001-2002           | 93,895 (12.5)      | 1272 (17.3)                   | 865 (17.3)                                 |
| 2002-2003           | 100,891 (13.5)     | 1343 (18.3)                   | 919 (18.4)                                 |
| 2003-2004           | 103,839 (13.9)     | 1168 (15.9)                   | 830 (16.6)                                 |
| 2004-2005           | 108,568 (14.5)     | 1292 (17.6)                   | 888 (17.7)                                 |
| 2005-2006           | 113,669 (15.2)     | 1101 (15.0)                   | 717 (14.3)                                 |
| 2006-2007           | 112,712 (15.1)     | 943 (12.8)                    | 629 (12.6)                                 |
| 2007-2008           | 115,104 (15.4)     | 232 (3.2)                     | 158 (3.2)                                  |
|                    |                    |                                | 39 (2.9)                                   |
| Birth weight, g     |                    |                                | 11 (2.8)                                   |
| <1000              | 2264 (0.3)         | 79 (1.1)                      | 46 (0.9)                                   |
| 1000-1499          | 3294 (0.4)         | 112 (1.5)                     | 84 (1.7)                                   |
| 1500-2499          | 23,748 (3.2)       | 372 (5.1)                     | 266 (5.3)                                  |
| 2500-4199          | 621,115 (83.0)     | 5796 (78.8)                   | 3973 (79.4)                                |
| 4200-               | 96,819 (12.9)      | 970 (13.2)                    | 623 (12.4)                                 |
| Missing data        | 1438 (0.2)         | 22 (0.3)                      | 14 (0.3)                                   |
| Size for gestational week |                |                                | 7 (0.5)                                    |
| Small (SGA)        | 16,048 (2.1)       | 355 (4.8)                     | 246 (4.9)                                  |
| Average (AGA)      | 706,891 (94.4)     | 6684 (90.3)                   | 4565 (91.2)                                |
| Large (LGA)        | 25,739 (3.4)       | 312 (4.2)                     | 195 (3.9)                                  |
| Missing data        | -                  |                                | 5 (0.1)                                    |
| Length of pregnancy, w |                |                                | 2 (0.2)                                    |
| <2                  | 7121 (1.0)         | 192 (2.5)                     | 119 (2.4)                                  |
| 2-3                 | 38,649 (5.2)       | 494 (6.7)                     | 338 (6.8)                                  |
| 4-7                 | 644,795 (86.1)     | 6021 (81.9)                   | 4102 (81.9)                                |
| ≥8                  | 57,798 (7.7)       | 646 (8.8)                     | 442 (8.8)                                  |
| Missing data        | 315 (0.0)          | 8 (0.1)                       | 5 (0.1)                                    |
| Mother age, year    |                    |                                | 2 (0.2)                                    |
| <2                  | 11,779 (1.6)       | 130 (1.8)                     | 75 (1.5)                                   |
| 21                  | 94,900 (12.7)      | 971 (13.2)                    | 602 (12.0)                                 |
| 25-29              | 222,375 (29.7)     | 2149 (29.2)                   | 1394 (27.9)                                |
| 30-34              | 261,366 (34.9)     | 2575 (35.0)                   | 1818 (36.3)                                |
| 35-39              | 131,080 (17.5)     | 1291 (17.6)                   | 944 (18.9)                                 |
| ≥40                | 27,174 (3.6)       | 235 (3.2)                     | 173 (3.5)                                  |
| Missing data        | 4                  | -                             | -                                          |
| Mother smoking      |                    |                                | -                                          |
| No                 | 642,436 (85.8)     | 6142 (83.5)                   | 4207 (84.0)                                |
| 1-9 cigarettes/d    | 42,618 (5.7)       | 471 (6.4)                     | 297 (5.9)                                  |
| ≥9 cigarettes/d     | 16,562 (2.2)       | 188 (2.6)                     | 103 (2.1)                                  |
| Missing data        | 47,062 (6.7)       | 550 (7.5)                     | 399 (8.0)                                  |
| Parents’ education  |                    |                                | 82 (6.0)                                   |
| >12 years           | 413,452 (55.2)     | 3842 (52.3)                   | 2814 (56.2)                                |
| 10-12 years         | 270,838 (36.2)     | 2863 (38.9)                   | 1738 (34.7)                                |
| <10 years           | 26,082 (3.5)       | 279 (3.8)                     | 183 (3.7)                                  |
| Missing data        | 38,306 (5.1)       | 367 (5.0)                     | 271 (5.4)                                  |
| Unemployed parents  |                    |                                | 48 (3.5)                                   |
| No                 | 624,497 (83.4)     | 6179 (84.1)                   | 4221 (84.3)                                |
| Yes                | 98,932 (13.2)      | 934 (12.7)                    | 599 (12.0)                                 |
| Missing data        | 25,249 (3.4)       | 238 (3.2)                     | 186 (3.7)                                  |
| Income, quintile    |                    |                                | 22 (1.6)                                   |
| Q5 (highest income) | 133,171 (17.8)     | 1457 (19.8)                   | 1135 (22.7)                                |
| Q4                 | 133,173 (17.8)     | 1354 (18.4)                   | 972 (19.4)                                 |
| Q3                 | 133,167 (17.8)     | 1399 (19.0)                   | 896 (17.9)                                 |
| Q2                 | 133,162 (17.8)     | 1421 (19.3)                   | 811 (16.2)                                 |

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eFigure 1. Cumulative incidence of cryptorchidism (diagnosis) among 748,678 Swedish boys, by two-year birth cohorts (2001-2014). Follow-up is until end of 2014.
| Cryptorchidism treatment | Yes n (%) | Relative incidence Lower | Hazard ratio (95% confidence interval) | P-value |
|--------------------------|-----------|--------------------------|----------------------------------------|---------|
| **Birth weight (gram)**  |           |                          |                                        |         |
| ELBW<1000 gram           | 79 (3.5)  |                          | 3.94 (3.15 to 4.92)                   | <0.001  |
| VLBW1000-1499 gram       | 112 (3.4) |                          | 3.70 (3.07 to 4.46)                   |         |
| LBW1500-2499 gram        | 372 (1.6) |                          | 1.69 (1.52 to 1.88)                   |         |
| Normal 2500-4199 gram    | 5796 (0.9)|                          | 1                                      |         |
| Heavy 4200 gram          | 970 (1.0) |                          | 1.06 (0.99 to 1.13)                   |         |
| **Size for gestational age** |         |                          |                                        | <0.001  |
| Small (SGA)              | 355 (2.2) |                          | 2.38 (2.14 to 2.65)                   |         |
| Average (AGA) (ref)      | 6684 (0.9)|                          | 1                                      |         |
| Large (LGA)              | 312 (1.2) |                          | 1.26 (1.13 to 1.42)                   |         |
| **Length of pregnancy**  |           |                          |                                        | <0.001  |
| <32 weeks                | 182 (2.6) |                          | 2.77 (2.39 to 3.21)                   |         |
| 32-36 weeks              | 494 (1.3) |                          | 1.36 (1.24 to 1.49)                   |         |
| 37-41 weeks (ref)        | 6021 (0.9)|                          | 1                                      |         |
| >42 weeks                | 646 (1.1) |                          | 1.19 (1.10 to 1.29)                   |         |
| **Maternal smoking**     |           |                          |                                        | 0.13    |
| No smoking (ref)         | 6142 (1.0)|                          | 1                                      |         |
| 1-9 cigarettes/d         | 471 (1.1) |                          | 1.09 (0.99 to 1.19)                   |         |
| >9 cigarettes/d          | 6801 (1.0)|                          | 1.08 (0.93 to 1.25)                   |         |
| **Age of mother (years)**|           |                          |                                        | 0.35    |
| <20                      | 130 (1.1) |                          | 1.08 (0.91 to 1.29)                   |         |
| 20-24                    | 971 (1.0) |                          | 1.05 (0.98 to 1.14)                   |         |
| 25-29                    | 2149 (1.0)|                          | 0.99 (0.93 to 1.04)                   |         |
| 30-34 (ref)              | 2575 (1.0)|                          | 1                                      |         |
| 35-39                    | 1291 (1.0)|                          | 1.02 (0.95 to 1.09)                   |         |
| >39                      | 235 (0.9) |                          | 0.92 (0.81 to 1.06)                   |         |
| **Education (years)**    |           |                          |                                        | 0.002   |
| >12 (ref)                | 3842 (0.9)|                          | 1                                      |         |
| 10-12                    | 2863 (1.1)|                          | 1.08 (1.02 to 1.13)                   |         |
| <10                      | 279 (1.1) |                          | 1.15 (1.02 to 1.30)                   |         |
| **Employment**           |           |                          |                                        | 0.53    |
| Yes (ref)                | 6179 (1.0)|                          | 1                                      |         |
| Unemployment             | 934 (0.9) |                          | 1.02 (0.95 to 1.10)                   |         |
| **Income (quintiles)**   |           |                          |                                        | 0.15    |
| Q5, highest income (ref) | 1440 (1.1)|                          | 1                                      |         |
| Q4                       | 1421 (1.1)|                          | 0.98 (0.91 to 1.05)                   |         |
| Q3                       | 1399 (1.1)|                          | 0.96 (0.90 to 1.04)                   |         |
| Q2                       | 1354 (1.0)|                          | 0.93 (0.87 to 1.01)                   |         |
| Q1, lowest income        | 1457 (1.1)|                          | 1.02 (0.95 to 1.10)                   |         |
| **Financial support**    |           |                          |                                        | <0.001  |
| No support (ref)         | 6381 (1.0)|                          | 1                                      |         |
| Support                  | 779 (1.1) |                          | 1.15 (1.07 to 1.24)                   |         |
| **Parents born in Sweden**|         |                          |                                        | <0.001  |
| Two (ref)                | 5063 (1.0)|                          | 1                                      |         |
| One                      | 962 (0.9) |                          | 1.06 (0.99 to 1.14)                   |         |
| None                     | 1324 (1.1)|                          | 1.37 (1.29 to 1.46)                   |         |

*Extremely low birth weight. Very low birth weight. Low birth weight.

eFigure 2. Childhood Incidence of cryptorchidism, hazard ratio by risk factors and socioeconomic variables. Bivariate logistic models, adjusted for year of birth.
**eFigure 3. Timing of surgery among children treated for cryptorchidism.** The cumulative proportion, by non-adjusted levels of travel time to hospital. Children born in Sweden 2001-2014, followed until 5 years of age.
| Treated for cryptorchidism at age 3 | Treated at age 3, n (%) | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|-------------------------------------|------------------------|--------------------|----------------------------------------|---------|
|                                     |                        | Earlier            |                                        |         |
| Travel time to treating hospital (minutes) |                       |                    |                                        |         |
| By each 30-minutes increase |                        |                    |                                        |         |
| By categories                      |                        |                    |                                        |         |
| <30 (ref)                          | 2946 (58.8)            |                    | 0.91 (0.88 to 0.95)                    | <0.001 |
| 30-59                               | 736 (53.8)             |                    | 0.84 (0.77 to 0.91)                    |         |
| 60-89                               | 207 (53.5)             |                    | 0.72 (0.62 to 0.82)                    |         |
| >90                                 | 364 (62.9)             |                    | 0.84 (0.76 to 0.94)                    |         |
| Education (years)                  |                        |                    |                                        | 0.001   |
| >12 (ref)                          | 2319 (60.4)            |                    | 1                                      |         |
| 10-12                              | 1549 (54.1)            |                    | 0.90 (0.84 to 0.96)                    |         |
| <10                                | 153 (54.8)             |                    | 0.82 (0.70 to 0.97)                    |         |
| Full employment                    |                        |                    |                                        | 0.003   |
| Yes (ref)                          | 3564 (57.7)            |                    | 1                                      |         |
| No                                 | 554 (59.3)             |                    | 0.87 (0.80 to 0.95)                    |         |
| Income (quintiles)                 |                        |                    |                                        | <0.001  |
| Q5, highest income (ref)           | 855 (59.4)             |                    | 1                                      |         |
| Q4                                 | 817 (57.5)             |                    | 0.87 (0.79 to 0.95)                    |         |
| Q3                                 | 801 (57.3)             |                    | 0.79 (0.72 to 0.87)                    |         |
| Q2                                 | 789 (56.4)             |                    | 0.86 (0.78 to 0.95)                    |         |
| Q1, lowest income                  | 821 (56.4)             |                    | 0.76 (0.69 to 0.84)                    |         |
| Financial support                  |                        |                    |                                        | <0.001  |
| No support (ref)                   | 3725 (58.4)            |                    | 1                                      |         |
| Support                            | 412 (52.9)             |                    | 0.81 (0.73 to 0.90)                    |         |
| Parents born in Sweden             |                        |                    |                                        | 0.15    |
| Two (ref)                          | 2859 (56.5)            |                    | 1                                      |         |
| One                                | 597 (62.1)             |                    | 1.07 (0.98 to 1.17)                    |         |
| None                               | 802 (60.6)             |                    | 0.96 (0.89 to 1.04)                    |         |

**Figure 4.** Relative incidence of treatment for cryptorchidism before 3 years of age, and hazard ratio by travel time to treating hospital and socioeconomic determinants. Bivariate Cox regression model adjusted for year of birth, without adjustment for risk factors.
Sensitivity analysis of main associations

The estimated hazard ratio for treatment by levels of travel time did not change substantially when travel time was presented as categories on the nominal scale (<30 minutes travel time being reference, the adjusted HR for 30-59 minutes travel time: 0.82 [95% CI 0.75 to 0.90]; adjusted HR for 60-89 minutes: 0.72 [95% CI 0.62 to 0.83]; and adjusted HR for 90 minutes or more: 0.84 [95% CI 0.74 to 0.95], p<0.001 for overall variable contribution). Later in the study period, more children had a longer travel time to hospital (eTable 1). Robustness of the results by the introduction of Nordic guidelines in 2007 were therefore tested by splitting the cohort in two, based on year of birth (2001-2006 and 2007-2014). This resulted in similar hazard ratios (by each 30-minute increase in travel time for children born 2001-2006; adjusted HR 0.90 [95% CI 0.83 to 0.96], p=0.003, and for children born 2007-2014; adjusted HR 0.92 [95% CI 0.88 to 0.96], p<0.001). The main association was also robust to changes in age cut-off in the survival analysis (eFigures 5 and 6). In fact, the relative incidence of being treated was even higher at age 2 years (treatment rate by each 30-minute increase in travel time: adjusted HR 0.87 [95% CI 0.83 to 0.91], p<0.001) and remained at age 5 years (adjusted HR 0.96 [95% CI 0.92 to 1.00], p=0.03). The main association remained robust also when length of pregnancy and maternal age at birth were kept as continuous variables using cubic splines instead of categories on the nominal scale; the estimated hazard ratio for treatment by levels of travel time did not changed at all (as seen when comparing Figure 4 in main article with eFigure 7).

| Treatment for cryptorchidism at age 2 | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|---------------------------------------|---------------------|----------------------------------------|---------|
| Travel time to hospital (minutes)     |                     |                                        |         |
| By each 30-minute increase             |                     | 0.87 (0.83 to 0.91)                    | <0.001  |
| Education (years)                      |                     |                                        |         |
| >12 (ref)                              |                     |                                        | 0.48    |
| 10-12                                 |                     | 0.95 (0.87 to 1.03)                    |         |
| <10                                    |                     | 0.96 (0.77 to 1.21)                    |         |
| Employment                             |                     |                                        | 0.19    |
| Yes (ref)                              |                     |                                        |         |
| Unemployment                           |                     | 0.92 (0.81 to 1.04)                    |         |
| Income (quintiles)                     |                     |                                        | <0.001  |
| Q5, highest income (ref)               |                     |                                        |         |
| Q4                                     |                     | 0.84 (0.74 to 0.94)                    |         |
| Q3                                     |                     | 0.72 (0.64 to 0.82)                    |         |
| Q2                                     |                     | 0.85 (0.75 to 0.96)                    |         |
| Q1, lowest income                      |                     | 0.78 (0.67 to 0.91)                    |         |
| Financial support                      |                     |                                        | 0.02    |
| No support (ref)                       |                     |                                        |         |
| Support                                |                     | 0.81 (0.68 to 0.97)                    |         |
| Parents born in Sweden                 |                     |                                        | 0.64    |
| Two (ref)                              |                     |                                        |         |
| One                                    |                     | 1.05 (0.93 to 1.18)                    |         |
| None                                   |                     | 1.05 (0.92 to 1.19)                    |         |

eFigure 5. Sensitivity analysis. Hazard ratio of treatment for cryptorchidism before 2 years of age, by travel time to treating hospital and socioeconomic determinants. Multivariable Cox regression model adjusted for year of birth and risk factors (birth week, size for gestational age, maternal smoking and age). Children born 2001-2014, followed 24 months from birth.
| Treatment at age 5 | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|--------------------|---------------------|---------------------------------------|---------|
| Travel time to hospital (minutes) | | | |
| By each 30-minute increase | Later | 0.95 (0.92 to 0.98) | 0.001 |
| Education (years) | | | |
| >12 (ref) | | 1 | |
| 10-12 | | 0.99 (0.93 to 1.06) | |
| <10 | | 0.95 (0.80 to 1.12) | |
| Employment | | | |
| Yes (ref) | | 1 | |
| Unemployment | | 0.94 (0.86 to 1.03) | |
| Income (quintiles) | | | |
| Q5, highest income group (ref) | | 1 | |
| Q4 | | 0.90 (0.83 to 0.99) | |
| Q3 | | 0.83 (0.75 to 0.91) | |
| Q2 | | 0.89 (0.80 to 0.98) | |
| Q1, lowest income | | 0.88 (0.78 to 0.98) | |
| Financial support | | | |
| No support (ref) | | 1 | |
| Support | | 0.84 (0.74 to 0.95) | |
| Parents born in Sweden | | | |
| Two (ref) | | 1 | |
| One | | 1.04 (0.95 to 1.14) | |
| None | | 1.03 (0.94 to 1.14) | |

**eFigure 6. Sensitivity analysis.** Hazard ratio of treatment for cryptorchidism before 5 years of age, by travel time to treating hospital and socioeconomic determinants. Multivariable Cox regression model adjusted for year of birth and risk factors (birth week, size for gestational age, maternal smoking and age). Children born 2001-2014, followed 60 months from birth.
| Treatment for cryptorchidism at age 3 | Timing of treatment | Hazard ratio (95% confidence interval) | P-value |
|--------------------------------------|---------------------|---------------------------------------|---------|
| Travel time to hospital (minutes)    | Later               | 0.95 (0.92 to 0.98)                   | <0.001  |
| By each 30-minute increase           |                     |                                       |         |
| Education (years)                    |                     |                                       |         |
| >12 (ref)                            |                     | 1                                     |         |
| 10-12                                |                     | 0.99 (0.93 to 1.06)                   |         |
| <10                                  |                     | 0.95 (0.80 to 1.12)                   |         |
| Employment                           |                     |                                       | 0.19    |
| Yes (ref)                            |                     |                                       |         |
| Unemployment                         |                     | 0.94 (0.86 to 1.03)                   |         |
| Income (quintiles)                   |                     |                                       | <0.001  |
| Q5, highest income group (ref)       |                     | 1                                     |         |
| Q4                                   |                     | 0.90 (0.83 to 0.99)                   |         |
| Q3                                   |                     | 0.83 (0.75 to 0.91)                   |         |
| Q2                                   |                     | 0.89 (0.80 to 0.98)                   |         |
| Q1, lowest income                    |                     | 0.88 (0.78 to 0.98)                   |         |
| Financial support                    |                     |                                       | 0.03    |
| No support (ref)                     |                     |                                       |         |
| Support                              |                     | 0.84 (0.74 to 0.95)                   |         |
| Parents born in Sweden               |                     |                                       | 0.48    |
| Two (ref)                            |                     | 1                                     |         |
| One                                  |                     | 1.04 (0.95 to 1.14)                   |         |
| None                                 |                     | 1.03 (0.94 to 1.14)                   |         |

**eFigure 7. Sensitivity analysis.** Hazard ratio of treatment for cryptorchidism before 3 years of age, by travel time to treating hospital and socioeconomic determinants. No categorization of continuous variables. Multivariable Cox regression model adjusted for year of birth and risk factors (birth week, size for gestational age, maternal smoking and age). Children born 2001-2014, followed 36 months from birth. Birth week and maternal age treated as continuous variables and analyzed with cubic splines. Departure from linearity may be important in the case of birth week (F-test: p=0.05), and overall the variable is likely to improve in the model (F-test: p=0.002). In the case of maternal age, there is likely no departure from linearity (p=0.57) and no overall contribution to the model (p=0.30).