STUDY QUESTION: Is there evidence at the population level of associations between different male genital disorders, outside Scandinavian countries?

SUMMARY ANSWER: At an international scale, there is evidence for a number of correlations between rates of four male reproductive disorders (hypospadias, cryptorchidism, testicular cancer and low sperm concentration).

WHAT IS KNOWN ALREADY: Some associations between these outcomes have been shown in studies focusing on individuals and mainly in Nordic European countries. These associations, together with histological evidence of a dysgenesis pattern in testicular tissue specimens, have generated the concept of the existence of a ‘testicular dysgenesis syndrome’ originating in utero.

STUDY DESIGN, SIZE, DURATION: This is a geographical correlation study using cancer, malformations rates and sperm quality data collected between the years 1998 and 2005.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Incidence rates of testicular cancer were extracted from International Agency for Research on Cancer registries and Globocan, while cryptorchidism and hypospadias prevalence rates were obtained from EUROCAT and International Clearinghouse for Birth Defects Surveillance and Research registries. Sperm concentration data were extracted from recent studies using standardized methodology. A total of 39 registries and 9 sperm studies were selected. Non-parametric Spearman correlation tests were used to test the association between these four disorders. Correlations were computed for all registries together, for registries with high-quality matching coverage only and by continents. Sensitivity analyses were also conducted using data from prospective clinical studies to take into account potential bias related mainly to ascertainment of malformation rates.

MAIN RESULTS AND THE ROLE OF CHANCE: We found positive correlations between testicular cancer and hypospadias ($r = 0.32$, $P = 0.05$) and between hypospadias and cryptorchidism ($r = 0.70$, $P = 0.008$). Stronger correlations were observed when using registries with high-quality matching coverage. Among these registries, differences between Europe and the rest of the world appeared (the positive correlation between testicular cancer and cryptorchidism was stronger outside Europe, $r = 0.83$, $P = 0.01$ compared with 0.40, $P = 0.60$ for European registries). A negative correlation between testicular cancer and sperm concentration was observed ($r = -0.88$, $P = 0.002$). These correlations support our initial hypothesis but remain only suggestive due to the intrinsic limitations in the study design (i.e. geographical correlation study) and do not allow causal inference.

LIMITATIONS, REASONS FOR CAUTION: Differences in the ascertainment of malformations rates (definition, length of follow-up) make the international comparison difficult. The small number of registries for some conditions (cryptorchidism) or of studies (for sperm quality) and the absence of information about major risk factors such as ethnicity and socioeconomic status in the registries are also limitations.

WIDER IMPLICATIONS OF THE FINDINGS: Our findings are in agreement with results of studies focusing on individuals and suggest that shared risk factors are present in the populations studied.

1 These authors contributed equally to this work.

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**Introduction**

There is increasing concern that in the Northern hemisphere, the two most common disorders of the male sexual differentiation, undescended testis (also called cryptorchidism) and hypospadias (a midline fusion defect of the male ventral urethra resulting in an abnormal location of the urethral meatus) are becoming more prevalent (Toppapi et al., 1996; Jegou et al., 1999). In parallel, marked geographical differences have been described for the incidence of testicular cancer (Curado et al., 2007; Chia et al., 2010), for the values of semen characteristics (Fédération Française des CECOS et al., 1997; Jørgensen et al., 2002) and for rates of cryptorchidism and hypospadias (Paulozzi, 1999; Toppapi et al., 2001). Interpretation of this geographical and temporal fluctuation of male reproductive health indicators has been partly attributed to variation of environmental factors but this remains controversial (Olesen et al., 2007; Foresta et al., 2008; Hsieh et al., 2008; Martin et al., 2008; Wang and Baskin, 2008; Main et al., 2010; Makarov and Hoigaard, 2010). The Scandinavian studies have generated substantial debate about whether or not there are etiological links between semen quality, testicular cancer, cryptorchidism and hypospadias, and these four elements have been suggested to be all symptoms of a common underlying testicular dysgenesis, named testicular dysgenesis syndrome (TDS) (Skakkebaek et al., 2001; Jørgensen et al., 2010). In particular, there has been substantial debate around the comparison between Denmark and Finland as a striking ‘mirror’ type of image: the semen concentration of young men is relatively low in Denmark but high in Finland and, in contrast, the incidence of cryptorchidism, hypospadias and testicular cancer are lower in Finland than in Denmark (Virtanen et al., 2001; Jørgensen et al., 2002, 2006; Boisen et al., 2004, 2005; Jacobsen et al., 2006). In this work, we widen the geographical comparative approach using data from countries other than Denmark and Finland.

**Materials and Methods**

Regional and national population-based registries were used to obtain incidence data for testicular cancer and prevalence data for congenital anomalies at birth (hypospadias and cryptorchidism). To obtain reliable and comparable data, we used those from organizations which have carefully selected, reviewed and evaluated the quality of registries for diverse geographic regions. Sperm quality data were extracted from recently published studies which employed standardized methodology.

**Cancer incidence data**

Cancer incidence rates were obtained from the last report of the International Agency for Research on Cancer, Cancer Incidence in Five Continents (CISC) (Curado et al., 2007). This document reports cancer incidence rates for the period 1998–2002 in 225 countries/regions worldwide. Additional data, not present in CISC, were extracted from the Globocan 2002 database which provides national estimates for all countries of the world derived from mortality and survival data and rates from subnational cancer registries. Estimates for 2002 are based on data available 2–5 years earlier. The Globocan 2002 software and database were downloaded from http://www-dep.iarc.fr/website. Geographical variation of morbidity associated with testicular cancer was recorded as region-specific incidence rates (per 100,000 persons per year) standardized for age using the world population.

**Congenital anomalies prevalence data**

Prevalence rates for hypospadias were obtained from the European Surveillance of Congenital Anomalies (EUROCAT) database. Cryptorchidism is not registered in this database. EUROCAT handles 43 population-based registries in 20 European countries and covers >25% of European Union births (http://www.eurocat-network.eu/). If a baby/fetus has several anomalies, EUROCAT registers each type of anomaly in the calculation of prevalence. Since 2005, all types of hypospadias have been included in this database (minor anomalies, such as glandular hypospadias, were excluded before 2005). Because of this change in the definitions of the anomalies, only data registered between 2005 and 2008 were extracted. The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) also reports prevalence rates for various malformations for different populations of the world. Hypospadias and cryptorchidism rates were collected for countries/regions for which there were no EUROCAT data. We used the registries of 2005 of the report available on the internet (at http://www.icbdsr.org/ published in 2007). We did not include the rate of cryptorchidism available for northern Netherlands as this anomaly is registered in this region only when combined with other defects.

From both sources we included cases diagnosed among live births, stillbirths and terminations of pregnancy. The rates of hypospadias and cryptorchidism extracted are prevalence rates per 10,000 births (live and still).

We also collected data from six prospective clinical studies of full-term male babies published in 1998 or later. These studies were conducted in Malaysia (Thong et al., 1998), Italy (Ghirri et al., 2002), Denmark (Boisen et al., 2004), Finland (Boisen et al., 2004), Lithuania (Preiksa et al., 2005) and the UK (Acerini et al., 2009). Correlations using rates of cryptorchidism at birth obtained in these clinical studies were used in separate sensitivity analyses (see the section Statistical analysis).

**Sperm quality data**

No registry collecting data from different geographical regions was identified for measures of sperm characteristics. To facilitate comparison, we collected sperm concentration data from published studies in the general population (usually young healthy men, between 18 and 20 years old, attending a compulsory medical examination for military service) and having used standardized methodology, involving similar inclusion criteria, questionnaires, record forms for physical examination and equivalent protocols for assessing sperm concentration and analysing results. We did not use data from studies performed among fertile men (partners of pregnant women) as they do not reflect the situation.
in general population: infertile men and subfertile men are under-
represented or not included in those studies and thus the results of
semen characteristics are inevitably higher. General population data
were available for nine European cities: Turku, Finland; Oslo, Norway; Co-
penhagen, Denmark; Tartu, Estonia (Jorgensen et al., 2002), Malmo, Sweden
(Richthoff et al., 2002); Riga, Latvia (Tsarev et al., 2005); Kaunas, Lithuania (Punab et al., 2002); Almeria, Spain (Fernandez et al., 2012) and Leipzig, Germany (Paasch et al., 2008).

Matching health data
Cancer and malformation rates do not necessarily correspond to the same
geographical areas. For instance, some cancer registries cover a whole
country, whereas the malformations registry covers only a region of that
country. We thus classified the registries into two groups based on their
geographic descriptions. The correspondence of selected cancer and con-
genital malformation registries is shown in Table I.

A first group (called ‘high-quality matching coverage’) contains registries
for cancer and congenital anomalies covering the same geographical area.
The second group (named ‘10%-matching coverage’) includes those situa-
tions where the malformations registry covers at least 10% of the popula-
tion (or total births) in the area covered by the corresponding cancer
registry (or vice versa). For example, the malformation registry Austria
Styria corresponds to the region of Styria which contains 14.7% of the
population covered by the Austria cancer registry. If the population (or
total births) was not available for the geographical zone covered by a regis-
try, we extracted the population for year 2005 from the EUROSTAT
website (http://epp.eurostat.ec.europa.eu). In some cases, calculations
were needed to match registries: we used the sum of cases and the
sum of total live births, stillbirths and terminations of pregnancy from
the three EUROCAT malformations registries of Ireland (Dublin, South
East and Cork-Kerry) to calculate one single rate to match the Ireland
cancer registry. A similar approach was used for the EUROCAT registries
Poland and Poland Wielkopolska to match the Poland cancer registry.

As data from sperm characteristics were available only for cities, they
were matched with the registry of the country or region where they are
located (except for Almeria which was matched with the registry of
Basque Country-Spain as no data from regional cancer and malformation
registries for the same time period and same geographical area were avail-
able in Southern Spain).

Statistical analysis
Non-parametric correlation tests (Spearman) were used to test the asso-
ciation between the rates and with median sperm concentration. We per-
formed correlations using all registries together and using only registries in
the ‘high-quality matching coverage’ category (providing better quality for
comparison due to the same geographical coverage for both cancer and
malformation outcomes). We then separated Europe and the rest of the
world. A number of sensitivity analyses were conducted to take into
account possible bias arising from varying inclusion criteria across birth
defects registries, especially relative to cryptorchidism. First, we selected
registries that included only cases diagnosed before 1 year of age and we
also used cryptorchidism rates obtained only from prospective clinical
studies. SAS software (SAS/STAT version 9.3; SAS Institute, Inc., Cary,
NC, USA) was used for statistical analyses.

Results
There were 39 registries selected and included in this study: 29 cover
European countries/regions, 4 are North American (USA and
Canada), 3 correspond to Australia and New Zealand, 2 to Latin
American countries and 1 covers a country in the Middle East
(Table I).

The rates of testicular cancer (39 registries) were higher in Western
Europe than in the rest of the world (Fig. 1). Eleven European countries
had rates >6.5 per 100 000 person-years with the highest values in
Norway, Denmark, Switzerland-Vaud, Germany-Saxony, Austria and
UK-England-Oxford. The lowest rates were in Latin American coun-
tries, in the Iberian Peninsula and in the Baltic countries.

A total of 36 registries contained data for hypospadias. Mainly
Oceania (Australia Victoria, Australia Western, New Zealand) and some European countries (Czech Republic, Hungary, Croatia)
presented the highest rates (>22.3 per 10 000 total births). The rate
was below 10 per 10 000 births in: Costa Rica, USA Georgia
Atlanta, Spain Basque Country, Italy North East, UK Northern
England, USA Utah, Portugal South, Poland and UK England Oxford.

Data for cryptorchidism were collected from only 13 registries and
the rates were very different: lower rates of <3.5 per 10 000 births,
in Italy Tuscany, USA Georgia Atlanta and Cuba and higher rates
(>54 per 10 000 births) in Australia and New Zealand.

Standardized studies of sperm characteristics in the general popula-
tion allowing comparison between geographic regions were available
only for European registries (Fig. 2). Men of the Baltic cities (Riga,
Tartu, Kaunas) and Spanish men from Almeria presented the highest
median sperm concentrations (≥55 × 10^6/ml). The values for men of
two Scandinavian cities (Turku and Malmo) were slightly lower and
the lowest concentrations corresponded to men from Leipzig,
Oslo and Copenhagen (≥42 × 10^6/ml).

For data from all registries combined, statistically significant positive
correlations were found between hypospadias and testicular cancer
(0.32, P = 0.05) and between cryptorchidism and hypospadias
(0.70, P = 0.008) (Fig. 3). When the analysis was restricted to data
from registries in the category ‘high-quality matching coverage’, the
correlation was stronger for hypospadias and testicular cancer (0.57,
P = 0.006) (Figs 3 and 4) and similar for cryptorchidism and hypospa-
dias (0.70, P = 0.01) (Figs 3 and 5).

Also, when restricting the analysis to registries of the ‘high-quality
matching coverage’ group, differences between Europe and the rest of
the world appeared. The same positive correlations presented
above were observed in non-European registries: between hypospa-
dias and testicular cancer (0.67, P = 0.05) and between cryptorchid-
ism and hypospadias (0.76, P = 0.03) but also between testicular
cancer and cryptorchidism (0.83, P = 0.01) (Fig. 6). No significant
associations were found for data from European registries.

When selecting only the eight registries with <1 year of follow-up
for cryptorchidism, we observed the following correlations: r = 0.62
(0.10) between testicular cancer and cryptorchidism [instead of
r = 0.53 (P < 0.10) using all cryptorchidism registries] and r = 0.60
(0.12) between hypospadias and cryptorchidism [instead of r =
0.70 (P < 0.01)]. Using data from six prospective clinical studies, we
found a correlation coefficient of r = 0.77 (P-value = 0.07) between
cryptorchidism and testicular cancer.

There was a significant negative correlation between sperm concen-
tration and testicular cancer (r = −0.88, P = 0.002) (Figs 3 and 7). No
other statistically significant association between sperm concentra-
tion and other outcomes was found in this analysis. However, the
available data were insufficient to evaluate the association between
sperm characteristics and cryptorchidism.
### Table I  Cancer incidence rates, congenital anomalies prevalence rates and sperm parameters in selected registries/studies.

<table>
<thead>
<tr>
<th>Cancer registry name: congenital malformation registry name</th>
<th>Cancer registry</th>
<th>Source</th>
<th>Ref. time period</th>
<th>Testicular Source</th>
<th>Ref. time period</th>
<th>Hypospadias</th>
<th>Cryptorchidism</th>
<th>Sperm concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia Victoria CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>5.5</td>
<td>ICBDSR 2005</td>
<td>33.5</td>
<td>54.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia Western CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>5.3</td>
<td>ICBDSR 2005</td>
<td>24.6</td>
<td>16.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium Antwerp CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>3.6</td>
<td>EUROCAT 2005–2008</td>
<td>18.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada Alberta CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>5.2</td>
<td>ICBDSR 2005</td>
<td>22.5</td>
<td>22.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada British Columbia CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>4.5</td>
<td>ICBDSR 2005</td>
<td>18.6</td>
<td>30.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costa Rica CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>2.6</td>
<td>ICBDSR 2005</td>
<td>4.9</td>
<td>8.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuba CI5C</td>
<td>Globocan</td>
<td>1998–2002</td>
<td>0.6</td>
<td>ICBDSR 2005</td>
<td>10.2</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>3.7</td>
<td>EUROCAT 2005–2006</td>
<td>15.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary CI5C</td>
<td>Globocan</td>
<td>1998–2002</td>
<td>5.6</td>
<td>ICBDSR 2005</td>
<td>28.7</td>
<td>18.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy Romagna Region CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>5.0</td>
<td>EUROCAT 2005–2008</td>
<td>14.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malta CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>4.0</td>
<td>EUROCAT 2005–2008</td>
<td>27.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>6.8</td>
<td>ICBDSR 2005</td>
<td>23.9</td>
<td>58.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slovak Republic CI5C</td>
<td>CISC</td>
<td>1998–2002</td>
<td>6.6</td>
<td>ICBDSR 2005</td>
<td>20.9</td>
<td>7.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Category A: same population covered by both registries (cancer and malformation)

Australia Victoria CI5C 1998–2002
Australia Western CI5C 1998–2002
Belgium Antwerp CI5C 1998–2002
Canada Alberta CI5C 1998–2002
Canada British Columbia CI5C 1998–2002
Costa Rica CI5C 1998–2002
Cuba CI5C 1998–2002
Czech Republic CI5C 1998–2002
Finland CI5C 1998–2002
Germany Saxony CI5C 1998–2002
Hungary CI5C 1998–2002
Italy Romagna Region CI5C 1998–2002
Malta CI5C 1998–2002
New Zealand CI5C 1998–2002
Norway CI5C 1998–2002
Poland CI5C 1998–2002
Slovak Republic CI5C 1998–2002

Median sperm concentration: don't know.
Table I

Continued

<table>
<thead>
<tr>
<th>Cancer registry name: malformation registry name</th>
<th>Source</th>
<th>Ref. time period</th>
<th>Testicular Source</th>
<th>Ref. time period</th>
<th>Hypospadias</th>
<th>Cryptorchidism*</th>
<th>City, country</th>
<th>Ref. time period</th>
<th>Sample size</th>
<th>Participation rate (%)</th>
<th>Median sperm concentration (10^6/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA Georgia Atlanta</td>
<td>CISC</td>
<td>1998–2002</td>
<td>3.7</td>
<td>ICBDSR 2005</td>
<td>3.7</td>
<td>3.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA Utah</td>
<td>CISC</td>
<td>1998–2002</td>
<td>5.4</td>
<td>ICBDSR 2005</td>
<td>6.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Category B: at least 10% of the population of one registry is covered by the other


Israel: Israel                                   | CISC   | 1998–2002       | 3.8              | ICBDSR 2005       | 29.2        |                |                |                  |            |                       |                                      |


Italy North East: Italy North East               | CISC   | 1998–2002       | 5.0              | ICBDSR 2005       | 3.4         |                |                |                  |            |                       |                                      |
<table>
<thead>
<tr>
<th>Country/Area</th>
<th>Time Period</th>
<th>CI5C</th>
<th>Time Period</th>
<th>EUROCAT</th>
<th>CI5C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estonia</td>
<td>CI5C 1998–2002</td>
<td>2.5</td>
<td>Tartu, Estonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1977–1999</td>
<td>104</td>
</tr>
<tr>
<td>Latvia</td>
<td>CI5C 1998–2002</td>
<td>2.1</td>
<td>Riga, Latvia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2005</td>
<td>133</td>
</tr>
<tr>
<td>Lithuania</td>
<td>CI5C 1998–2002</td>
<td>1.9</td>
<td>Kaunas, Lithuania&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1997–1999</td>
<td>196</td>
</tr>
</tbody>
</table>


<sup>a</sup>Source of data: ICBDSR, 2005.


<sup>c</sup>Jørgensen et al. (2002).

<sup>d</sup>Paaß et al. (2008).


<sup>f</sup>Hypospadias is counted combined with epispadias.


<sup>h</sup>Fernandez et al. (2012).

<sup>i</sup>Richthoff et al. (2002).

<sup>j</sup>Tsarev et al. (2005).

<sup>k</sup>Punab et al. (2002).
Discussion

There has been no previous analysis of the possible associations between rates of different affections or abnormalities of the male urogenital tract on such a large international scale. In addition to the intrinsic limitations of geographic correlation analysis compared with individual studies (Elliot et al., 1992), our analysis suffered from a number of limitations resulting from the diverse geographic scales, numbers and quality of available data.

The different geographic scales at which international data are collected (country, region, city) present a particular difficulty for overlap between cancer rates, malformation rates and sperm characteristics. Regional variability within countries has been documented for some of them (Fédération Française des CECOS, 1997; Nori et al., 2002; Aho et al., 2003; INVS, 2011a,b). Consequently, the choice of registries used in our study had to take into account both data availability at the smallest geographical scale (to account for regional variations) and the quality of the geographical correspondence (areas covered) between cancer and malformation registries.

Despite the systematic review process of data used in the present study, there were still some heterogeneities that might have influenced our findings, such as the definition of the outcomes, inclusion criteria or time periods. For example, the definition of hypospadias has changed over the years (Dolk et al., 2004) and registered rates for cryptorchidism are difficult to compare (Toppari et al., 2001) due to the complexities related to its assessment. Nevertheless, the results of the sensitivity analyses conducted either by selection of registries including only cases of cryptorchidism diagnosed before 1 year of age, or using data from prospective clinical studies of male newborns confirm the correlations observed in all registries except for a decrease in the statistical power in some instances. This loss of statistical power is partly due to the smaller number of observations, but also to the fact that several of the excluded registries from Oceania or Canada have the highest rates reported among ICBDSR registries included in our analysis. These high rates may be partly due to the inclusion of the so-called acquired cryptorchidism cases (Acerini et al., 2009; Wohlfahrt-Veje et al., 2009), but may also be the result of a genuine greater incidence in these countries.

Another limitation is that the data on sperm characteristics are known to vary according to the methodology used to collect them and that studies are somewhat limited by the relatively low participation rates (Cohn et al., 2002). Consequently, our policy of including only best-quality and comparable data lead to numerous otherwise relevant registries and studies being excluded from our analysis. This resulted in the number of registries being too small for detailed analysis of possible variations related to different regions in the world, or to take into account imprecision in rates related to different population sizes. In addition, most registries do not contain associated

Figure 1 Testicular cancer incidence rates (age-standardized world per 100 000) and hypospadias prevalence rates (per 10 000 total births) in selected registries. Sources: CISC, Globocan, EUROCAT, ICBDSR, GADM and EUROSTAT.
descriptive data concerning relevant characteristics of the populations, for example the ethnic group or socioeconomic status. Such factors condition disease rates and may modify the strength of associations, as illustrated when studying separately Europe and the rest of the world. Our approach was also limited by the time period selected. Geographical differences in cancer rates may relate to environmental events decades ago, whereas differences in malformation rates could be consequences of recent environmental conditions. The potential environmental component of the observed correlations between rates could therefore be interpreted as attributable to steady changes in environment occurring in the last 20–30 years. Additionally, spatial comparison at a given time period does not take into account the different temporal trends in rates in the various countries or regions studied (Jørgensen et al., 2011, 2012). Its validity is therefore based on the underlying assumption that, despite dynamic changes in time, relative spatial variations between regions or countries will remain the same.

In spite of these methodological limitations, our study provides evidence of geographical correlations among rates of the studied disorders of the male reproductive system.

The geographical differences in the rates of testicular cancer have already been described (Curado et al., 2007) and can be explained in part by differences in the ethnic makeup of the populations. A number of suspected risk factors for testicular cancer have been studied including occupational exposures, socioeconomic factors or personal history of cryptorchidism. These results, except for history of cryptorchidism, have to be confirmed as the studies were limited by low statistical power (INSERM 2008; Richardson et al., 2012).

Our analysis consistently identified positive correlations between hypospadias and cryptorchidism, and between testicular cancer and hypospadias. It has previously been suggested that hypospadias and cryptorchidism are associated and share a number of risk factors, including intrauterine growth disorders (preterm birth, low birthweight and small for gestational age) (Toppari et al., 2010). Additionally, there is some evidence that men with a personal history of hypospadias have an increased risk of testicular cancer (Prener et al., 1996; Schnack et al., 2010).

The positive significant correlation found between testicular cancer and cryptorchidism among ‘high-quality matching coverage’ registries outside Europe is consistent with studies showing a markedly higher.
The negative association found between testicular cancer and sperm concentration is also compatible with data showing that fathers subsequently diagnosed with testicular cancer having smaller numbers of children (Møller and Skakkebaek, 1999; Baker et al., 2005) and that there is a higher risk of testicular cancer in men with impaired fertility (Jacobsen et al., 2000; Roeth et al., 2000; McLachlan et al., 2007; Walsh et al., 2009). We were unable to test for associations between cryptorchidism and sperm quality since only two regions had simultaneous data for these disorders.

Environmental factors, and particularly exposure to hormone-disruptive chemicals, are believed to contribute to the increasing rates and geographical variations recently observed for male reproductive disorders. Exposure to some organochlorine compounds, which are persistent pollutants with long half-lives, including polychlorinated biphenyls and dichloro-diphenyl-trichloroethane and its metabolites, have been studied in various parts of the world: exposure has been associated with testicular cancer but not with cryptorchidism, hypospadias or fertility (Cook et al., 2011). A meta-analysis concluded the existence of an association between maternal and paternal occupational exposure to pesticides and a higher risk of hypospadias (Rocheleau et al., 2008). Increased rates of cryptorchidism and hypospadias were also observed in diethylstilbestrol (DES)-exposed human subjects (Gill et al., 1979; Stillman, 1982) and possibly in infants exposed to external sex hormones as reviewed by Toppari and Skakkebaek (1998). Accordingly, both cryptorchidism and hypospadias were found to be induced in mice exposed in utero to DES (Newbold and McLachlan, 1985). Furthermore, phthalates which are ubiquitously present in the environment have been shown not only to suppress the rat fetal testosterone production but also to induce abnormalities in the development of the rat male genital tract including cryptorchidism and hypospadias (Mylchreest et al., 1998, 2002; Fisher et al., 2003;
Chauvigné et al., 2009, 2011). Phthalates have also been found to be associated with defects in reproductive markers in humans, indicative of an androgen deficiency (Swan et al., 2005, 2008; Pant et al., 2008; Meeker et al., 2009; Joensen et al., 2012; Suzuki et al., 2012).

Our work is a systematic correlation study of the four reproductive male health markers worldwide. Some regions were not represented as they did not have data satisfying the inclusion criteria. Geographical correlations of valid comparable data can be interpreted as reflecting the existence of a direct etiological link between two conditions (and in that case such a link is likely to be confirmed in individual studies) or suggest shared risk factors possibly interacting with other factors present in the various populations studied. However, this does not guarantee that the geographical variations observed can be attributed to differences in the intrinsic risks of populations, rather than differences in diagnosis or reporting practices. Like all correlation studies, our analysis suffers from significant limitations with respect to causal

Figure 5 Hypospadias and cryptorchidism prevalence rates (per 10,000 total births) for registries in the high-quality matching coverage group.

Figure 6 Testicular cancer incidence rates (age-standardized world per 100,000) and cryptorchidism prevalence rates (per 10,000 total births) for registries in the high-quality matching coverage group.
inference; however, our findings reinforce the notion that the four components of the TDS concept are indeed associated at the population level.

Authors’ roles
T.S. participated in the design of the study, data collection, statistical analysis and drafting the manuscript. C.C. contributed to selecting and exploiting the statistical methods, analysis and critical discussion. L.M. contributed to the discussion and interpretation of the findings. S.C. and B.J. contributed equally to the design of the study, analysis, drafting and critical discussion. All authors have read and approved the final version of the manuscript.

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Conflict of interest
None declared.

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