

## REVIEWS



# Environmental factors in declining human fertility

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**Abstract** | A severe decline in child births has occurred over the past half century, which will lead to considerable population declines, particularly in industrialized regions. A crucial question is whether this decline can be explained by economic and behavioural factors alone, as suggested by demographic reports, or to what degree biological factors are also involved. Here, we discuss data suggesting that human reproductive health is deteriorating in industrialized regions. Widespread infertility and the need for assisted reproduction due to poor semen quality and/or oocyte failure are now major health issues. Other indicators of declining reproductive health include a worldwide increasing incidence in testicular cancer among young men and alterations in twinning frequency. There is also evidence of a parallel decline in rates of legal abortions, revealing a deterioration in total conception rates. Subtle alterations in fertility rates were already visible around 1900, and most industrialized regions now have rates below levels required to sustain their populations. We hypothesize that these reproductive health problems are partially linked to increasing human exposures to chemicals originating directly or indirectly from fossil fuels. If the current infertility epidemic is indeed linked to such exposures, decisive regulatory action underpinned by unconventional, interdisciplinary research collaborations will be needed to reverse the trends.

Are human populations living in industrialized regions at risk of a catastrophic decline? With anthropogenic (that is, caused by humans or their activities, such as emission of greenhouse gases) climate change firmly placed on the global agenda, there is increasing concern that human populations (alongside those of many other species) are at risk, unless drastic adjustments are implemented to ensure more sustainable living. What is less evident on sustainable development agendas, however, is that more than half of all humans presently live in areas of the world where birth rates have persistently declined below the levels necessary to reproduce and sustain their populations<sup>1</sup> (FIG. 1). Transnational migration has historically had a role in the ebb and flow of population change, and rising life expectancy has tempered population declines in many places<sup>1</sup>. However, with birth rates having dropped below one per woman in some East Asian countries/regions<sup>2</sup>, it is imperative that we understand why, how and with what consequences ongoing fertility declines are taking place.

Of note, the word 'fertility' has two meanings in modern literature. Although it can sometimes be confusing,

the proper meaning is usually evident from the context in which the word is being used. In demography, fertility is defined as the number of children (for example, low fertility equals low fertility rates) and in biology, fertility is defined as fecundity, or the ability to reproduce. In addition, the term fertility rate is often used synonymously with total fertility rate (TFR; the average number of live births a woman would have by the age of 50 years if she were subject throughout her life to the age-specific fertility rates observed in a given year; its calculation assumes that there is no mortality) or the general fertility rate per 1,000 persons (that is, the number of births in a year divided by the number of women aged 15–44 years times 1,000).

The underlying causes of the current unsustainable fertility rates are unclear; however, demographic research has provided some evidence of socioeconomic causes<sup>3</sup>, which have been investigated in two large international studies<sup>1,4</sup>. A crucial and unanswered question is, however, whether fecundity (the biological ability to conceive) is indeed constant (as generally indicated in

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**Key points**

- Industrialized regions have birth rates so low that their populations cannot be sustained; declines in birth rates are generally ascribed to socioeconomic and cultural factors, although human infertility is widespread.
- Decreasing fertility rates were already recorded around 1900 in Denmark, a few decades after the beginning of utilization of fossil fuels that were, and still are, drivers of modern industrialization and wealth.
- We hypothesize that declines in fertility rates might be linked to exposures to chemicals originating from fossil fuels causing human reproductive problems and cancer; early gestation might be a sensitive period.
- The current unsustainable birth rates will eventually result in decreasing populations.
- A key research challenge remains: how to distinguish biological from socioeconomic and behavioural factors?

demographic publications) or whether modern lifestyles have resulted in changes in human reproductive physiology resulting in societies with a greater number of infertile, or even sterile, couples than previously.

Here, we discuss trends in human reproductive behaviour and health that are associated with infertility (that is, failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse<sup>5</sup>), including impaired semen quality, rising incidence of testicular cancer, delays in couples' pregnancy planning and trends in assisted reproduction. The fact that the changes have occurred over a period of only a couple of generations suggests that environmental factors have a role. We link these trends to modern lifestyles in industrialized regions. Reviewing existing evidence, we find support for the idea that some of the unfavourable reproductive trends started more than 100 years ago.

**Fertility rates**

A well-documented, although unexplained, pronounced decline in fertility rates began in Europe, including Denmark, around the year 1900 (REFS<sup>6–8</sup>) (FIG. 2). However, as depicted in FIG. 2, both world wars (World War I and World War II) interrupted the decline. In Denmark, whereas the impact of World War I was short, the increase in fertility rates that started during World War II levelled off and then persisted until modern

contraception was introduced in Denmark in the 1960s<sup>9</sup>. A similar pattern was seen in Sweden<sup>10</sup>. It is noteworthy that in other parts of the world (Supplementary Fig. 1), where the onset of industrialization and economic upturn started much later than in many European countries/regions (for example, in many South American countries/regions), the observed fertility decline appeared within the past five decades.

In the countries/regions with early industrialization (that is, starting in the 1800s), a decline in fertility rates occurred through the 1900s, although interruptions occurred during world crises, including periods of war and economic depression<sup>6–8</sup>. These trends have resulted in marked demographic changes. In some parts of the world, including Japan (Supplementary Fig. 2) and Germany, the number of children and adolescents has declined by 50% since the 1960s<sup>11</sup>. During the same period, life expectancy has markedly increased in these and other places<sup>12</sup>. As a result, there are now considerably fewer young people and relatively more elderly people in industrialized regions than previously, creating so-called ageing societies. In the future, these demographic trends will undoubtedly result in decreasing populations in many countries/regions<sup>1</sup>. However, there is a considerable time lag. In Japan, where unsustainable fertility rates were observed as early as 1961, the population size did not peak until 2009, when deaths eventually exceeded births in the transformed and aged Japanese population (Supplementary Fig. 2)<sup>13</sup>.

**Lifestyles and environmental exposures**

Industrial development of a society is associated with fundamental changes in daily life, including altered work processes and new lifestyles, which are often associated with increased sedentary behaviour and weight gain, in addition to the increasing risk of exposure to industrial toxins<sup>14</sup>. Importantly, increased use of fossil fuels, which has historically been closely associated with industrialization of a society, accelerated with industrialization in the late 1800s, when improved standards of living became possible for many people due to the increased use of fossil fuels for home heating and transport<sup>15,16</sup>. New environmental exposure patterns also occurred. Initially, these exposures were often in the form of the smog that is well known from London and Los Angeles in the 1900s<sup>15</sup>. Currently, smog has also been seen in cities with high economic growth in the past few years (for example, in numerous Chinese cities<sup>16</sup>). In addition, industrialization has profoundly changed habits of consumption, including diet, clothing and travel<sup>17</sup>. These changes in human life have globally improved living standards and made daily life more comfortable for many people; however, they have also resulted in increased exposure to new synthetic chemicals<sup>18</sup>, all originating — directly or indirectly — from fossil fuels<sup>19</sup>.

A crucial question is whether the changes in lifestyle and environment that are associated with industrialization are causing changes to the reproductive physiology of humans that are so extensive that a tipping point<sup>20</sup> has been reached where sustainable human reproduction is threatened.

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### Factors that influence birth rates

#### Contraception, unplanned pregnancies and abortions

The availability of effective contraception, and especially the introduction of the contraceptive pill in the 1960s<sup>21</sup>, has greatly facilitated family planning and has also had a role in improved educational attainments of women (that is, girls and women are staying in education for longer than previously), which is clearly linked to reduced fertility rates<sup>1</sup>. However, the decline in the number of births per woman had already begun around 1900, half a century before the introduction of the contraceptive pill<sup>22</sup>. In fact, the Danish fertility rate was already as low as two children per woman in the 1930s<sup>8</sup> (FIG. 2). Despite the availability of effective contraceptive methods, approximately half of all pregnancies in the USA were unplanned during the period 2008–2011, whilst in the early 1980s almost 60% of all pregnancies in the USA were unplanned<sup>23</sup>. Although these numbers are most probably overestimates by up to 6% due to the method of measurement used<sup>24</sup>, it remains to be elucidated whether the declining rate of unintended pregnancies in the USA was due to more careful use of contraception than in the 1980s.

A high proportion of unplanned pregnancies are continued to term, although a fraction result in induced abortion<sup>23</sup>. It is noteworthy that the declining birth rate is not due to an increased number of induced abortions, as in most industrialized regions with declining birth rates the curves for abortions have also been declining<sup>25,26</sup>. Our own studies show that the decline in the ‘natural

conception rate’ (births plus induced abortions, minus births after medically assisted reproduction (MAR)) among women in Denmark is even more pronounced than the decline in fertility rate<sup>27,28</sup>.

A comparative analysis of pregnancy data from Scandinavian countries/regions for the period 1975–2013 showed stable and similar delivery rates of around 60 per 1,000 women aged 15–44 years and fertility rates between 1.5 and 2.0 per woman<sup>29</sup>. However, during the same period, the frequency of induced abortions was clearly declining in Denmark and Finland, slightly decreasing in Norway, but increasing in Sweden. During the most recent 6-year period in the study, delivery and induced abortion rates were compared with the rate of hormonal contraceptive use. The latter was neither consistently associated with birth rates nor with induced abortion rates. Denmark, Sweden and Finland had the highest percentage use of hormonal contraception, the highest and lowest rate of induced abortions were seen in Sweden and Finland, respectively, and all countries/regions had similar rates of delivery. Thus, it seems that factors other than the use of hormonal contraception must have influenced the rather different induced abortion rates in these countries/regions.

#### Spontaneous pregnancy loss

A historical follow-up study from Denmark published in 2020 that assessed all recorded pregnancy losses in the country over a 40-year study period demonstrated that 23% of women in Denmark had been referred with a pregnancy loss at least once before the age of 45 years (18% had one loss, 4% two losses and about 1% had three or more losses)<sup>30</sup>. Notably, these numbers do not include losses never diagnosed at a hospital such as early losses, which are often not detected by the women themselves. The frequency of recorded pregnancy losses in Denmark increased from 7.5% in 1978–1979 to a peak at 10.7% in 2000, followed by a reduction to 9.1% in 2015–2017. What seems to have been a decrease since the year 2000 is probably just a reflection of changed clinical practice since 2000, when routine surgical evacuation of miscarriages ceased. Since this change, some women who have had a spontaneous miscarriage have not been referred to hospital, and therefore the miscarriage was not registered<sup>30</sup>. Data also suggest that unintended pregnancy loss has become more common in the USA with a relative increase of 1–2% per year since 1990 (REF.<sup>31</sup>).

#### Twinning rates

It has been hypothesized that spontaneous dizygotic twinning rates can be considered a proxy measure of combined high male and high female fertility as it reflects the frequency of double ovulation and fertilization<sup>32,33</sup>. The twinning rate (the proportion of twin deliveries in relation to the total number of deliveries, expressed per 1,000 deliveries) has varied significantly during the past 100 years. After 1930–1950 the proportion of twin deliveries declined to its lowest point in the 1970s, which is the period before the surge in assisted reproductive techniques (ART), including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), which are known factors favouring

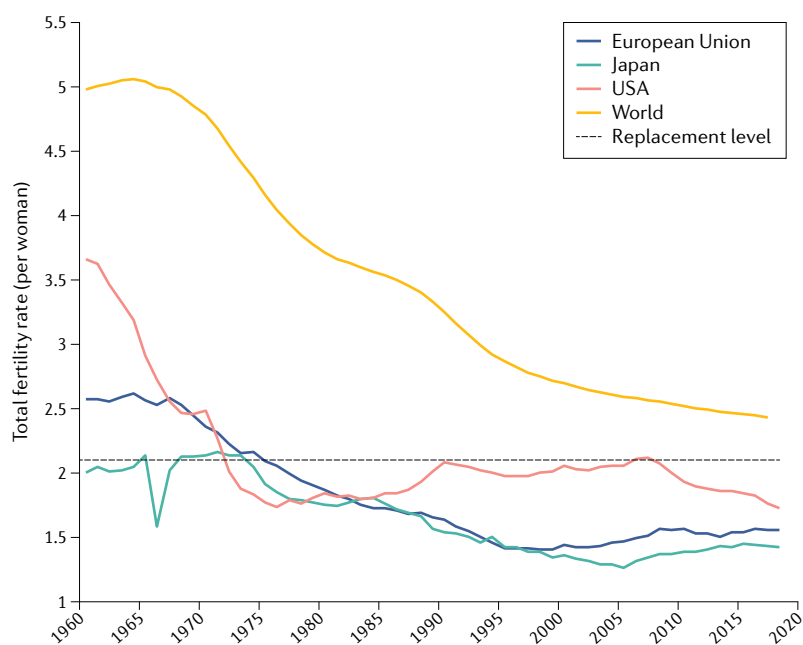
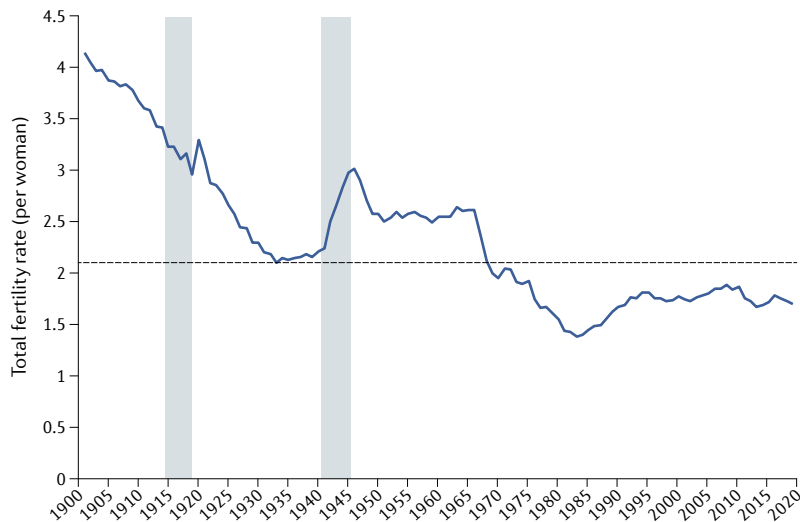


Fig. 1 | Total fertility rates in the European Union, Japan and the USA, 1960–2018.

The dashed line represents a fertility rate of 2.1, below which a population cannot be sustained (total fertility rate is the average number of children per woman). Despite higher birth rates in non-industrialized parts of the world, even the total fertility rate of the total world population seems to be declining towards 2.1. Additional information on trends in fertility rates in 43 countries across North America, South America, Europe, Asia and Africa, 1960–2019, is shown in Supplementary Figure 1. Data from [Databank, World Development Indicators](#); Country: European Union, Japan, USA; Series: Fertility rate, total (births per woman); time: 1960–2018.



**Fig. 2 | Total fertility rate, Denmark, 1901–2019.** The dashed line represents a fertility rate of 2.1 children per woman (below which a population cannot be sustained). Note that a downwards trend in total fertility rate started long before the introduction of the contraceptive pill in the 1960s. The trend was interrupted by World War I and World War II. The grey columns mark births conceived during World War I and World War II. Data from Statistics Denmark.

twinning due to the transfer of several fertilized eggs<sup>34</sup>. In fact, a significant proportion of twin deliveries (up to 73% of all twins since the introduction of ART in the 1980s<sup>34,35</sup>) might be due to ART.

When considering twinning rates before the introduction of ART, decreasing trends in twinning rates were apparently paralleled with a decrease in TFR in the same places in the world before 1980 (REFS<sup>8,34</sup>) (FIG. 2; Supplementary Fig. 1). Other factors might have contributed to the decline in twinning rates; for example maternal age, an important determinant of twinning rates as increased maternal age might be associated with an increase in twinning rate. Furthermore, a history of oral contraceptive use has been suggested to contribute by directly reducing the probability of double ovulation and fertilization<sup>36</sup>.

A Danish study found that the dizygotic twinning rates, adjusted for maternal age and parity, in Denmark in the period 1931–1965 declined by 29% compared with an overall total twinning rate decline of 22% in the same period<sup>37</sup>. The same group also found that rates stabilized in the period 1977–1981 (REF.<sup>38</sup>), in accordance with observed trends in most other countries/regions.

### Couple infertility and MAR

Human infertility is common in industrialized regions, as indicated by the increasing use of MAR<sup>39</sup>. The number of children born after MAR (IVE, ICSI, egg donation and insemination with donor sperm or partner sperm) has increased dramatically worldwide and the total number has now reached millions<sup>40,41</sup>. In Denmark, as many as 10% of all newborn babies are now conceived after MAR<sup>39,42</sup>. The need for MAR, including ART treatments, can be due to both female and male infertility, and often a combination of problems in both the female and the male partner is diagnosed<sup>39</sup>.

### Pregnancy planning

One of the major factors determining fertility rates across the industrialized world during the past 50 years has undoubtedly been the ability of women to have more control over their reproductive choices. With the advent of the oral contraceptive pill in the 1960s, millions of women have been able to reclaim autonomy over the timing of conception. Indeed, there was the intention, through donations and national commitments, that there should be 120 million new users of the oral contraceptive pill by 2020 (Family Planning 2020), which underpins the importance of the oral contraceptive pill for modern family planning.

The consequent risk from postponing family initiation is that the family size might ultimately be smaller than in previous generations due to the age-related decrease in fecundity. This change might be due to an intentional decision, but for others it might mean that they will never be able to reach their hoped for family size due to the limitations of the female reproductive window. However, it seems that many, but not all, women have insight into this fact<sup>43</sup>. Modelling has been undertaken to determine a woman's chance of having two children based on the age she starts trying to conceive, without and with the use of IVF if it is required<sup>44</sup>. This study showed that if a woman starts attempting to conceive at 37 years old, she would have a 60% chance of achieving her goal of two children; however, if she waited until she was 40 years old she would only have a 30% chance. If she aspired to having three children, and was prepared to use IVF technology if appropriate for her, to give her a 90% chance of having three children, she should start attempting to conceive at 28 years of age, which is considerably younger than the age the majority of women in developed nations start their family.

When couples postpone starting a family, the average paternal age will also increase, and semen quality, particularly motility of sperm, diminishes<sup>45,46</sup>. However, the fecundity decline is much more subtle in men than in women, as testicular function, including sperm production, is often maintained throughout life<sup>47</sup>. By contrast, as a woman ages, in line with a reduction in the number of ovarian follicles, there is a progressive reduction in normal ovulatory frequency<sup>48</sup>.

The often-cited main cause of a woman's reduced fecundity in her late 30s is poor egg quality. This catch-all term encapsulates the increased predisposition of the oocyte to aneuploidy, as a result of chiasmata proximal to the telomere becoming more susceptible to mis-segregation, which is attributable to an age-related progressive loss of cohesion proteins<sup>49,50</sup>. Additionally, with a progressive reduction in mitochondrial function, less ATP is available for spindle formation, microtubular activity and polar body extrusion, which promotes aneuploidy<sup>50</sup>. Furthermore, it is believed that the oocyte is at greater risk of epigenetic modification as a woman ages<sup>48</sup>. The increased risk of aneuploidy not only leads to a reduction in fecundity, but also to an increased predisposition to miscarriage, which understandably causes distress and might further delay attempts at conception<sup>50</sup>. Oocyte quality starts to rapidly decline for women beyond 37 years of age, which is reflected in



the stark reduction in the success rates of IVF treatment (Supplementary Fig. 3)<sup>51,52</sup>.

Thus, the delay in pregnancy intention is assumed to be responsible for many cases of female infertility. By contrast, solid data on age-specific fertility rates in Denmark since 1901 suggest that more women in their late 30s and 40s were able to carry pregnancies to term in 1901 than now, even without the availability of ART<sup>8</sup> (Supplementary Fig. 4). This finding could indicate that more couples nowadays might become subfertile with age than previously. Polycystic ovary syndrome (PCOS), which affects up to one in five women of reproductive age, is the most common female disorder leading to infertility<sup>53</sup>. However, there is no confirmed evidence that the incidence of PCOS or other diseases affecting the female reproductive system that lead to infertility are rising<sup>53</sup>. For instance, it is unclear whether the rate of endometriosis is increasing, as a result of the inherent difficulty of its diagnosis, which relies on a diagnostic laparoscopy<sup>54</sup>. By contrast, solid evidence shows increases in the incidence of male reproductive disorders, including testicular cancer and poor semen quality (see subsequent sections). Nevertheless, studies on the aetiology of changing human fecundity should take both female and male factors into account.

Since the 1990s, there has been an increased research focus on the possible link between changing exposures to multiple endocrine-disrupting chemicals and human reproductive health. Such studies are demanding, as numerous chemicals might be involved. In addition, animal data indicate that the female and the male partner might react differently to the same exposures<sup>55</sup>. Therefore, the importance of couple fecundity has been highlighted in prospective cohort designs, where eligible couples were followed after discontinuing contraception to try for pregnancy<sup>56</sup>. Alterations in couple fecundity were seen according to differences in urine or plasma concentrations of several endocrine-disrupting chemicals in both men and women, after adjusting for the partner's concentrations<sup>56–58</sup>. Importantly, the findings underscore the importance of a couple-based cohort design, which was used in a cluster of studies<sup>59–61</sup>.

### Male reproductive disorders

In contrast to the scarcity of available information about trends in female fertility issues (except trends in postponing pregnancy), there is a large amount of literature on adverse trends in male reproductive disorders. An important question is whether there are genetic or environmental factors that could explain why men are sensitive to changes in the environment. Several studies have shown genetic variation among strains of rats and mice in susceptibility to endocrine disruption by chemicals<sup>62–65</sup>. An important finding was that CD-1 mice and Sprague–Dawley rats, which have often been used in laboratories for testing chemical safety, might be less sensitive to endocrine disruption than other strains of rodents<sup>64–66</sup>. Interestingly, the CD-1 mice and Sprague–Dawley rats are also good breeders<sup>66</sup>. It has not been examined whether men are particularly prone compared with women to endocrine disruption due to environmental exposures. However, as shown in the following

sections, there are data demonstrating that the function of the human testis is inferior compared with that of other mammals.

### Poor human spermatogenesis

Sperm count is linked to the quality of spermatogenesis in the seminiferous tubules<sup>67</sup>. Compared with other mammalian species belonging to different orders, human spermatogenesis is uniquely poor<sup>68</sup> (TABLE 1).

Small animals typically allocate a greater proportion of body mass and energy to maintenance of the testes and sperm production than larger animals, which is also related to sexual behaviour and reproductive strategies<sup>69</sup>. Therefore, in general, species that have the largest gonadosomatic index (testis mass divided by body weight) also have the highest sperm production per gram of testis (known as spermatogenic efficiency; daily sperm production per gram of testis). For instance, as shown in TABLE 1, the gonadosomatic index in humans is approximately four to ten times lower than that in the black-tufted marmoset (*Callithrix penicillata*) and laboratory rodents<sup>68,70</sup>. In addition, the seminiferous tubules in humans occupy a lower percentage of the testicular volume than is seen in the laboratory animals included in the study<sup>68</sup>. Furthermore, the human testis capsule occupies a much higher percentage of the testis (~20%) than in rodents, such as mice (~4%), meaning that in humans there is much less volume devoted to testicular parenchyma<sup>68</sup>. Another important comparison is the Sertoli cell volume density. Although humans have a high number of Sertoli cells per gram of testis, these important somatic cells of the seminiferous epithelium display a very low capacity for germ cell support<sup>68</sup> (TABLE 1). In humans, Sertoli cells occupy a high proportion of the seminiferous epithelium (~40%), in contrast to mice in which this figure is much lower (~15%); thus, human testes have a reduced volume of germ cells. Therefore, not surprisingly, Sertoli cell volume density within the seminiferous tubule is inversely correlated with the efficiency of sperm production<sup>70</sup>.

The number of differentiated spermatogonial generations is another key parameter related to the magnitude of sperm production and is used in comparative studies among different species. In particular, the number of spermatogonial generations dictates the number of germ cells that enter meiosis, being characteristic of each species and phylogenetically determined. In humans, only two generations are observed (type A (dark and pale) and type B), meaning that only four germ cell divisions occur (two mitotic and two meiotic) before spermatids are formed, whereas eight exponential divisions take place in laboratory rodents and farm animals, such as bulls (*Bos taurus*) and boars (*Sus scrofa domesticus*) (TABLE 1). Moreover, in humans, in addition to apoptosis that normally occurs during the spermatogonial phase, germ cell apoptosis during meiosis results in almost 70% loss of spermatocytes<sup>68</sup>. This loss means that the overall rate of spermatogenesis in humans is sixfold and 30-fold lower than that observed in the marmoset (*C. penicillata*) and rats, respectively. Taking into consideration the spermatogonial kinetics, the meiotic divisions and germ cell loss during spermatogenesis in the

Table 1 | Testis function and reference semen parameters in humans and other mammalian species

Parameters	Human	Marmoset ( <i>Callithrix penicillata</i> ) <sup>224</sup>	Rat	Mouse <sup>225</sup>	Bull	Boar	Rabbit
<b>Testis</b>							
Testis weight (g) <sup>a</sup>	16.6	0.5	1.7	0.1	402	365	3.1
Gonadosomatic index (%) <sup>b</sup>	0.08	0.36	0.8	0.6–0.8	0.1	0.4	0.21
Seminiferous tubules (%)	62	92	86	91–93	73	83	87
Sertoli cells per gram of testis (×10 <sup>6</sup> )	49	35	40	55–64	28	20	25
<b>Spermatogenesis</b>							
Sertoli cell efficiency <sup>c</sup>	3.0	8.0	10	10–12	8.0	12	12
Spermatogonial generations <sup>d</sup>	2	4	6	6	6	6	5
Meiotic index <sup>e</sup>	1.3 (68)	3.5 (13)	3.4 (15)	3.0 (25)	3.6 (10)	3.2 (20)	3.3 (18)
Overall rate of spermatogenesis <sup>f</sup>	3.2 (80)	20 (63)	97 (62)	65 (75)	65 (75)	68 (73)	39 (69)
Spermatogenic cycle length (days)	16	15.4	12.9	8.6–8.9	13.5	9.0	10.9
Spermatogenesis total duration (days) <sup>g</sup>	72	69	58	39–40	61	41	49
Spermatogenic efficiency (×10 <sup>6</sup> ) <sup>h</sup>	4.1	18	24	38–53	12	24	25
<b>Epididymis</b>							
Epididymal sperm transit (days) <sup>72</sup>	5.5	NA	8–10	5–5.8	4–15	9–11.8	6.6–12.7
Epididymal sperm reserve (×10 <sup>9</sup> )	0.84	NA	0.74	0.08	57	161	2.1
<b>Ejaculate</b>							
Ejaculate volume (ml)	1–5	0.03	NA	NA	2–10	150–500	0.4–0.6
Sperm concentration (million per millilitre)	>20	1,063	NA	NA	300–2,000	25–300	230–350
Sperm per ejaculate (million)	>40	32	NA	NA	10,000	45,000	150
Motile sperm (%)	>50	83	77	69	40–75	50–80	81
Morphologically normal sperm (%)	>30	63	91	96	65–95	70–90	67

Unless otherwise stated the source of data for testis function and the epididymal sperm reserve data shown are from REF.<sup>68</sup> and REF.<sup>70</sup>; references related to semen evaluation: REFS<sup>226–232</sup>. NA, not available. <sup>a</sup>Right testis plus left testis divided by two. <sup>b</sup>Testis mass divided by body weight. <sup>c</sup>Number of round spermatids per Sertoli cell. <sup>d</sup>Number of differentiated spermatogonial generations that are usually type A, intermediate and type B. <sup>e</sup>Number of round spermatids per each primary spermatocyte (the numbers in parentheses show the percentage of germ cell loss based in the theoretical yield of four). <sup>f</sup>Number of spermatids formed per differentiated initial type A spermatogonia (the numbers in parentheses show the percentage of germ cell loss based on the theoretical yield for each species according to the mitotic divisions or generations from initial type A spermatogonia and the two meiotic divisions). <sup>g</sup>Assuming that spermatogenesis takes 4.5 cycles. <sup>h</sup>Daily sperm production per gram of testis.

human testis, only two spermatozoa are produced out of ten from each initial differentiated type A spermatogonia, whereas in other mammals this figure is three to four out of ten (see the overall rate of spermatogenesis in TABLE 1). Therefore, even producing 1,500 sperm with each heartbeat, human males have the least productive testes of all mammalian species so far investigated.

The duration of spermatogenesis in a species is determined by the length of the spermatogenic cycle, which is under the control of the germ cell genotype<sup>71</sup> and is an important determinant of the magnitude of sperm production. Species with shorter durations of spermatogenesis are usually those with a higher sperm production. This observation is well illustrated when comparing humans to rodents in TABLE 1.

The sperm transit time through the epididymis ranges from ~5 days to 16 days<sup>72</sup> in the mammalian species listed in TABLE 1. The frequency of semen collection does not influence this transit, and the time required for sperm maturation within the caput and corpus of the epididymis ranges from 2 days to 5 days. Therefore,

only a few days are required for sperm to develop their fertilizing potential in humans and mammals in general. As a clear illustration of inefficient spermatogenesis in humans, the epididymal sperm reserve is quite similar in humans and rodents, even though humans have much larger testes (TABLE 1). Finally, besides having a very low number of sperm output, human semen quality, including sperm morphology and motility, is generally worse than in the other mammals shown in TABLE 1. It remains to be investigated whether low spermatogenic efficiency makes human males more vulnerable to environmental exposures than farm animals and laboratory rodents.

**Semen quality.** In 1992, evidence of a decline in sperm concentration over half a century in Europe and the USA was reported<sup>73</sup>. However, the data remained controversial, even after 25 years. In 2017, a systematic review and meta-regression analysis on trends in human sperm count was published aiming to answer the question: have human sperm counts, as measured by sperm concentration and total sperm count, declined? A total of

244 estimates of sperm concentration and total sperm count, sampled in 1973–2011, were extracted out of 7,518 publications initially screened for meta-regression analysis<sup>74</sup> (FIG. 3).

There was a significant decline in sperm concentrations between 1973 and 2011 among ‘unselected Western’ men (−1.38 million per millilitre per year, 95% CI −2.02 to −0.74;  $P < 0.001$ ) and among fertile Western men (−0.68 million per millilitre per year, 95% CI −1.31 to −0.05;  $P = 0.033$ ). Among unselected Western men, the mean sperm concentration declined, on average, 1.4% per year with an overall decline of 52.4% between 1973 and 2011. Similarly, the decline in total sperm count in unselected Western men was on average 1.6% per year, with an overall decline of 59.3% within the study period. Fewer semen studies have been published from non-Western countries/regions. However, several studies have shown a remarkable decline in semen quality among sperm donors in China<sup>75,76</sup>. It is also noteworthy that some Chinese investigations have linked air pollution to changes in semen quality<sup>77</sup>.

In Denmark, a single-centre prospective study was initiated in 1996 to monitor semen quality among young men from the general population (still ongoing). Overall, the results indicate that during over 20 years of surveillance, semen quality in this population has been stable but low. More than one-third of the included men had ‘low’ semen quality, defined as having one or more semen parameters (sperm concentration, motility or morphology) below the WHO reference limits<sup>78</sup>. When comparing the data from this study to historical data of Danish men examined in an infertility clinic in the 1940s, the distribution of sperm concentration in this study was skewed to lower levels. Men examined in the 1940s had a median sperm concentration of more than 60 million per millilitre, whereas it was only 45 million per millilitre among the men examined around year 2000 (REF.<sup>79</sup>). Importantly, the method of assessing the

sperm concentration, based on the haemocytometer, did not differ between the two populations.

The chances of achieving a pregnancy in a given menstrual cycle are reduced if the sperm concentration is below approximately 40 million per millilitre<sup>80–82</sup> (Supplementary Fig. 5). Thus, in a population such as that of the men examined in the 1940s, only a small proportion of the men had a sperm concentration below the level where fecundity would be affected, and semen quality might have declined previously without any noticeable effect on men’s fertility. But with the level observed today, a large proportion of young men have a sperm concentration in the suboptimal range below the threshold of 40 million per millilitre and a longer time to pregnancy or need for fertility treatment could be expected<sup>20</sup>.

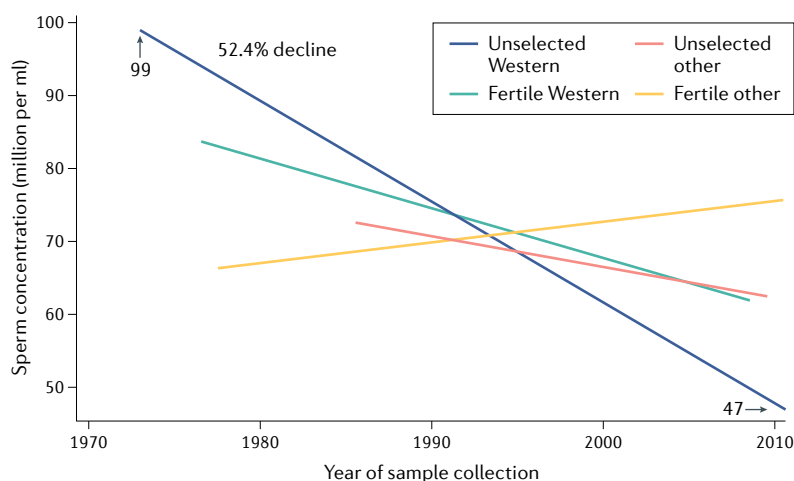
#### Significance of changes in reference ranges for human semen quality.

An evaluation of data on trends in semen quality might be hampered by the fact that normality in medicine is often defined as the range between the 2.5 and 97.5 percentiles in a random sample from the general population. The most recent WHO guidelines for analysis of semen adhere to this principle<sup>83</sup>. However, while this is a relevant approach for the most basic areas of human physiology (for example blood levels of sodium and potassium), this approach is not always appropriate in medical practice. As an example, the distribution of body mass among individuals in a population is heavily influenced by the type of diet. Using the 2.5 and 97.5 percentiles as limits of normality in a population with general over-nutrition might lead to ‘normal’ ranges that are too high, which from a health perspective is inappropriate. Similarly, there are historical data to suggest that ranges of normal semen quality according to WHO guidelines are not appropriate and should be updated, as too many men with low fecundity prospects might be evaluated as ‘normal’<sup>84</sup>. It is also noteworthy that according to the current WHO guidelines<sup>83</sup>, samples with as few as 5% morphologically normal sperms (95% abnormal) are categorized as within the ‘normal’ reference range (Supplementary Fig. 6).

#### Testicular cancer

As testicular cancer, which mainly occurs in young men, is associated with disorders such as undescended testis, decreased semen quality, infertility and childlessness, it is pertinent to include trends in this disease in a general discussion of trends in male reproductive health<sup>85</sup>.

A remarkable worldwide increase in the incidence of testicular cancer has taken place during the past 100 years. Ever since the establishment of national cancer registries, first initiated in 1943 in Denmark<sup>86</sup>, a significant worldwide increase in testicular cancer has been observed, particularly among white men<sup>87</sup>. Although the increasing trend was briefly interrupted in birth cohorts of Nordic men born during the world wars<sup>88,89</sup>, the incidence rates of testicular germ cell cancer in Denmark doubled between 1943 and 1962 (REF.<sup>86</sup>). However, it is not known when this secular trend started. Interestingly, historical mortality data from countries/regions with early industrialization onset, including England and



**Fig. 3 | Changes in average sperm concentrations 1973–2011.** The slopes of sperm concentration were estimated as a function of sample collection year using weighted meta-regression models, adjusted for predetermined covariates and modification by fertility (‘unselected by fertility’ versus ‘fertile men’) and geographic group (‘Western’, including North America, Europe, Australia and New Zealand, and ‘other’, including Asia, Africa and South America). Sperm concentrations declined significantly between 1973 and 2011. Figure reprinted with permission from REF.<sup>74</sup>, OUP.

the USA, show that the secular trend in testicular germ cell cancer mortality started as early as around 1900 (REFS<sup>90,91</sup>).

Currently, there are 74,500 estimated new testicular cancer cases per year globally<sup>92</sup>. While its contribution to overall cancer incidence is small (1%), testicular cancer is the most common cancer in young men aged 15–44 years in Europe, the Americas and Oceania<sup>92</sup>. One-third of all cases occur in Europe, with the highest age-standardized (world) incidence rates of >10/100,000 observed in Norway and Denmark<sup>92,93</sup>.

The secular trend is continuing, with testicular cancer incidence rates increasing worldwide, including in parts of Latin America and Asia that previously had very low incidence<sup>94,95</sup> (FIG. 4). In Europe, an attenuation of increasing incidence has been reported from the highest risk countries/regions, while the largest increases in rates have been observed in lower risk countries/regions, such as Finland, the Baltic countries/regions and some countries/regions in southern and eastern Europe<sup>95</sup>. Thus, the overall testicular cancer burden continues to increase in Europe, most notably in eastern Europe, with a 32% predicted increase in the number of cases between 2010 and 2035, as well as globally<sup>87</sup>.

### Possible biological mechanisms

#### *Roles of genetic and epigenetic factors*

To our knowledge, no single genetic or epigenetic factor has been shown to affect fertility on a population scale. Obviously, genetic or epigenetic factors negatively affecting fertility are not likely to survive in the population, but the increased use of MAR (as discussed already), and especially ICSI, bypasses the natural negative selection pressure, and enables the accumulation of genetic and epigenetic variants with subtle effects on fertility in the population. Hence, genetic and epigenetic variants with even subtle effects on fertility should be of concern, if they accumulate in the population.

**Genetic variants with effects on reproduction.** In men, two studies have identified variants (found near *DPY19L2* (REF.<sup>96</sup>) and *SPATA16* (REF.<sup>97</sup>)) associated with globozoospermia (a rare form of infertility in which the sperm cells are abnormal). However, genome-wide association studies (GWAS) in men with oligospermia (low sperm count) or azoospermia (no sperm) have been quite inconclusive. Very few variants overlap between the conducted studies<sup>98,99</sup>, which probably reflects the fact that the phenotype (male infertility) can be caused by a multitude of different factors. Sequencing initiatives have, therefore, started to identify rare mutations causing non-obstructive azoospermia, which is a more precisely defined phenotype<sup>100</sup>.

Mutations causing non-obstructive azoospermia have been identified in several genes<sup>101</sup>, but can only explain non-obstructive azoospermia in a small fraction of all cases. The largest known genetic effect on male fertility still relates to the sex chromosomes, X and Y, including microdeletions in the AZF regions on the Y chromosome and the presence of supernumerary X chromosomes, as found among men with Klinefelter syndrome<sup>99</sup>.

In female individuals, GWAS have investigated traits such as age at the birth of the first child and the number of children ever born (also influenced by social factors)<sup>102</sup>, self-reported age at menarche and menopause<sup>103,104</sup>, and anti-Müllerian hormone levels<sup>105</sup> as indirect measures of the ovarian reserve. In the study of anti-Müllerian hormone levels, only one variant reached significance (rs16991615) and this variant was also found to be associated with differences in age at menopause<sup>106</sup>. The rs16991615 variant is a missense variant located in exon 9 of *MCM8*, which is required for homologous recombination, and the variant might reduce repair of double strand breaks causing arrest of follicle development, as observed in *Mcm8*-knockout mice<sup>107</sup>. In general, several of the GWAS have indicated that DNA repair is critical for follicular development, but it is questionable whether an accumulation of such variants has occurred in the past five to ten decades and whether the modest effect sizes observed have any role in the observed decreasing fertility trends.

**Epigenetic variation and reproduction.** While the contribution of genetic factors to decreasing fertility trends is questionable, it is likely that epigenetic patterns can be affected in a time window encompassing three to four generations (corresponding to the period where decreasing fertility trends have been observed; see previous discussion). Epigenetic marks are dynamic and can be affected by lifestyle and environmental exposures, for example, and it is well-documented that epigenetic marks in the germline can be inherited and cause effects in the following generations<sup>108</sup>. The dynamic epigenetic patterns, however, also make it difficult to associate such marks with reproductive traits with certainty. The most studied epigenetic marks include methylation of the DNA strand at CpG sites and small RNAs.

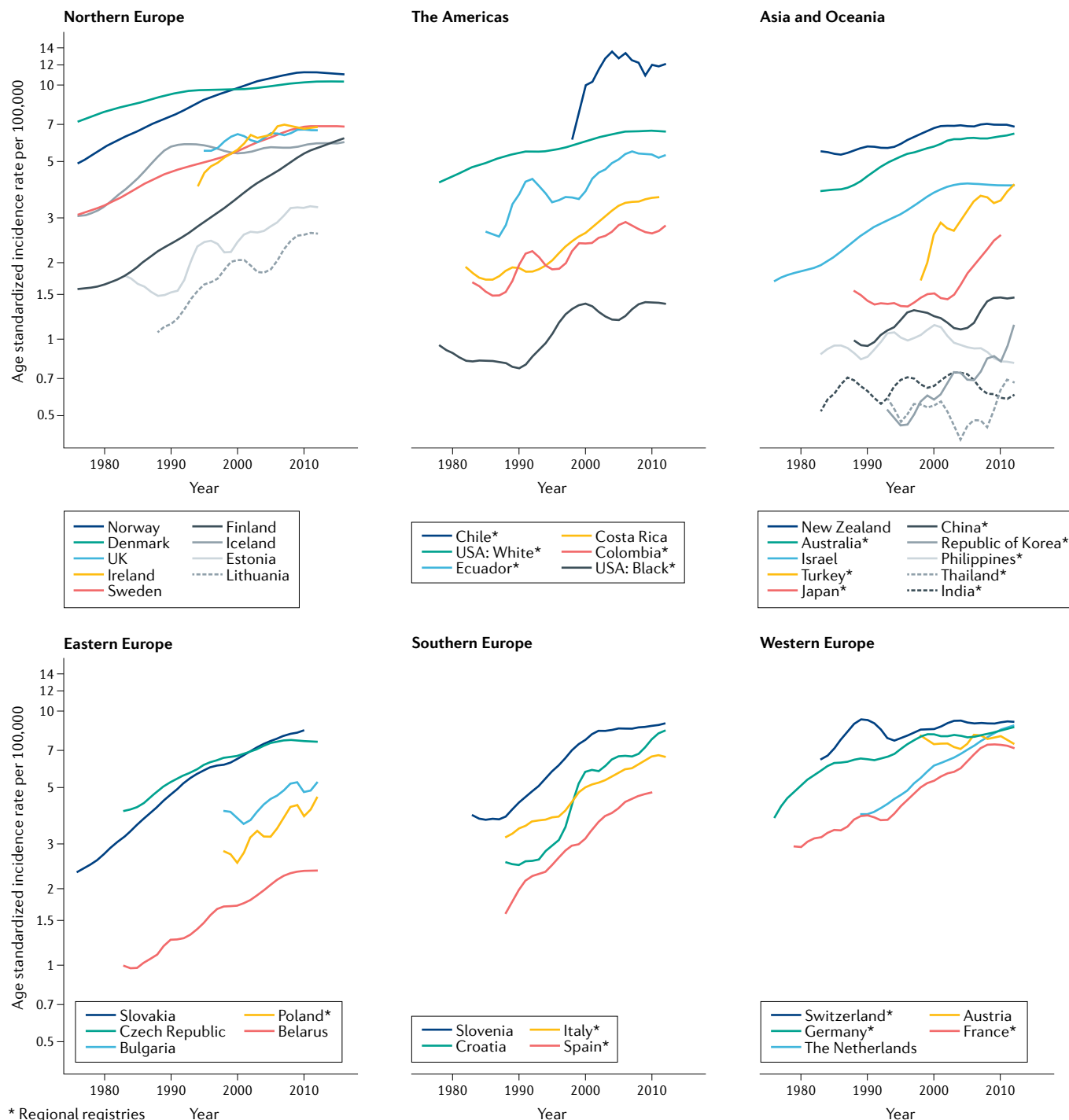
Changes in DNA methylation in blood samples have been associated with, for example, pubertal timing in both boys and girls<sup>109,110</sup> and with the average number of children a woman gives birth to<sup>111</sup>. DNA methylation marks have also been linked to lifestyle and environmental exposures<sup>112,113</sup>. Other studies have shown that effects of in utero exposure to famine<sup>114</sup> or maternal smoking during pregnancy<sup>115</sup> can be detected in the blood methylome in adult life. However, although such blood DNA methylation marks have been shown to be a proxy for alterations in reproductive tissues such as the testis<sup>109</sup>, it is currently unknown if alterations in germline DNA methylation have any effect on fertility. It is noteworthy that the ejaculate also contains somatic cells, which can affect measurements of DNA methylation marks in sperm<sup>116</sup>, and methylation marks are erased and reprogrammed in the preimplantation embryo. Nevertheless, several chemicals have been shown to be associated with alterations in the sperm methylome<sup>117–119</sup> in rats, in which changes in the sperm methylome can be observed in the third (F3) generation after exposure to the agricultural fungicide vinclozolin<sup>120</sup>.

Accumulating evidence indicates that small RNAs inside sperm can carry lifestyle and exposure information between generations<sup>108,121</sup> (FIG. 5). Although spermatozoa that leave the testis are unable to react to environmental



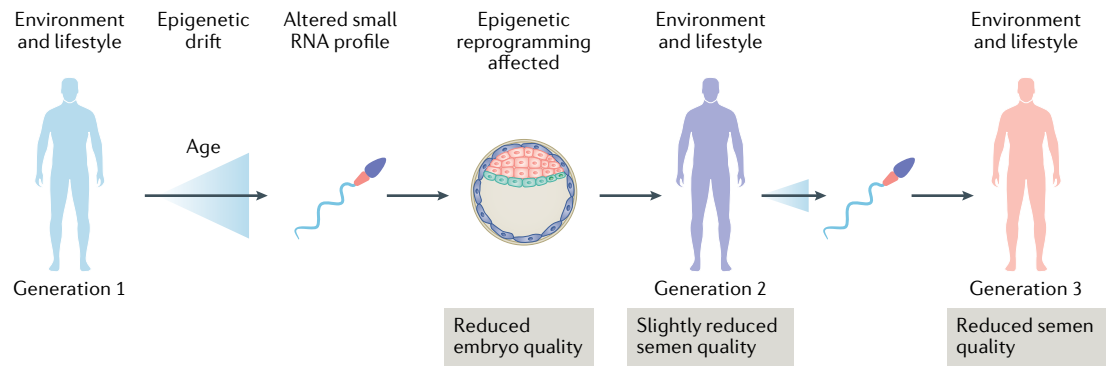
changes by transcription, they engulf extracellular vesicles during transit in the epididymis. These vesicles, called epididymosomes, are derived from somatic cells of the epididymal epithelia and contain both proteins and small RNAs<sup>122</sup>. Mouse studies have suggested that dietary

changes cause alterations in the small RNA content of the epididymosomes, which in turn can affect embryo development<sup>123</sup>. Direct injection of either sperm-derived or synthetic RNAs that are upregulated in the sperm of obese mice into fertilized eggs resulted in offspring with



**Fig. 4 | Testicular cancer incidence trends in selected countries/regions worldwide.** Note that the incidence rates are increasing globally and are generally highest in regions with white populations of European origin. Several subnational registries were used to produce national estimates for the figure: Australia (NSW, South Australia, Tasmania, Victoria, Western Australia), Chile (Valdivia), China (Shanghai, Hong Kong), Colombia (Cali), Ecuador (Quito), France (Calvados, Doubs, Isere), Germany (Saarland), India (Chennai), Italy (Modena, Parma, Ragusa,

Romagna), Japan (Miyagi, Nagasaki, Osaka), Korea (Seoul), Philippines (Manila), Poland (Kielce), Spain (Basque Country, Granada, Murcia, Navarra, Tarragona), Switzerland (Geneva, Neuchatel, St Gall-Appenzell), Thailand (Chiang Mai, Khon Kaen, Lampang, Songkhla), Turkey (Antalya, Izmir), UK (England, including East of England, East Midlands, North East, North West, London, South East, South West, West Midlands, and Yorkshire and the Humber; Scotland), US (SEER-Black, SEER-White). Figure adapted with permission from IARC<sup>94</sup>.



**Fig. 5 | Illustration of epigenetic drift.** Environment-mediated and lifestyle-mediated epigenetic drift in the germline might be passed on by small RNAs to subsequent generations. With increasing age of the individual, the sperm epigenome is likely to acquire a range of epigenetic alterations that can be passed on to subsequent generations. Although the concept has been established in animal models, it remains to be validated in humans.

glucose intolerance and obesity<sup>124</sup>. Small RNA-mediated changes are hence able to survive and potentially affect epigenetic reprogramming in the early embryo. Similarly, stress-induced changes in the small RNA profile of human sperm have been observed, albeit only in a limited number of studies<sup>121</sup>. In human sperm, the levels of a microRNA, miR-191-5p, have been correlated with both sperm morphology and embryo quality<sup>125</sup>. Hence, it is likely that both lifestyle and environmental exposure mediate changes in the sperm small RNA profile, which might affect health and fertility in subsequent generations. Such mechanisms could potentially accumulate across generations and theoretically have a role in the decreasing fertility rates.

**Advanced paternal age as a risk factor for genetic abnormalities in offspring.** Concern has been raised that increasing paternal age due to delays in pregnancy planning could result in an increase in the number of spontaneous mutations in sperm cells and lead to stillbirths, rare syndromes, cancer and mental health disorders in offspring<sup>126,127</sup>. Although each of such cases might be severe, the quantitative role of these rare mutations for reproductive health in general is minor.

**Gonadal dysgenesis**

It is well documented that synthetic toxins, including pesticides, can cause problems for adult reproductive functions when exposure occurs in adulthood; however, these changes are mainly reversible, even in individuals with azoospermia<sup>128–130</sup>. By contrast, fetal damage of the developmental processes of the gonad can cause permanent reproductive effects in adulthood, and potentially also congenital malformations such as cryptorchidism and hypospadias<sup>131</sup>. Adult consequences of fetal maldevelopment might be testicular cancer, spermatogenic disorders and infertility<sup>131</sup>.

It has been recognized for decades that the fetal testis of mammals is particularly sensitive to external exposures, including irradiation<sup>132–134</sup>, and landmark toxicological research has revealed that perinatal exposure to phthalates can cause reproductive symptoms in adult rats, including low testosterone levels, undescended testes, hypospadias and spermatogenic abnormalities<sup>135,136</sup>.

These symptoms seem to be related to a dysgenesis of the fetal testis, including abnormal development of Leydig and Sertoli cells (FIG. 6). Although the effects of phthalates on fetal gonads have been most extensively studied, antiandrogenic effects of several other endocrine disruptors on the fetal testis have also been observed. Interestingly, a masculinization programming window has been identified<sup>137–140</sup> during which disruption of the normal, endogenous sex hormone activity is irreversibly detrimental for the development of the male gonads and genitalia<sup>140</sup> (FIG. 6). Apart from phthalates, chemicals with the ability to displace androgens from the androgen receptor (that is, certain azole and imidazole pesticides, bisphenols and parabens) or to inhibit steroidogenic enzymes (that is, the pesticides prochloraz and linuron) can also negatively affect male sexual differentiation<sup>138</sup>. Other molecular pathways, such as a disrupted Sertoli cell differentiation via diminished prostaglandin levels caused by certain pain killers, or activation of the aryl hydrocarbon receptor by polychlorinated dioxins and biphenyls, also have a role<sup>141,142</sup>. There is experimental evidence that these pathways interact to produce mixture effects after combined exposure to these chemicals<sup>138</sup> (FIG. 6). Future comprehensive evaluations of the impact of chemical exposure on male reproductive health will have to consider the joint effects of phthalates, azole and imidazole pesticides, bisphenols, parabens, analgesics, polychlorinated dioxins and biphenyls and other endocrine-disrupting chemicals.

In addition, the fetal female reproductive system might be vulnerable<sup>143,144</sup>, although it seems to be less sensitive than the male reproductive system to environmental exposures, for example, to phthalates<sup>145</sup>. However, a group of biologists have proposed ten putative adverse outcome pathways relevant to female reproductive disorders to be considered in toxicological testing as an important step towards safeguarding the reproductive health of human females<sup>146</sup>.

**Gonadal dysgenesis and testicular cancer**

Most of the evidence on the reproductive effects of endocrine disruptors is derived from animal studies; however, there is also some human evidence that environmental exposures are associated with the development of

undescended testis, hypospadias, infertility and testicular cancer<sup>147–150</sup>. The strongest evidence of a fetal origin of male reproductive disorders comes from epidemiological investigations showing birth cohort effects with regard to the risk of developing germ cell cancer in young adulthood<sup>88,89</sup>. For instance, men born during World War II (and possibly also during World War I) turned out to have a decreased risk of germ cell cancer, which is in line with this theory<sup>88,89</sup>. During World War I and World War II, the increasing trends in consumption of fossil fuels were dramatically interrupted due to import restrictions and so the population was probably less exposed to pollution from coal and oil and other consumer products than previously (Supplementary Figs 7,8).

Migration studies, where populations move between areas with different risks of testicular cancer, are also in line with the hypothesis that testicular cancer is of fetal origin: the country/region where an individual is born determines the risk, even if the individual migrates as a

child<sup>151–153</sup>. Furthermore, studies of the precursor cells of germ cell cancer (germ cell neoplasia in situ) have shown that they have characteristics of fetal gonocytes<sup>154</sup> and also express the same fetal markers as normal fetal gonocytes, including OCT4 and NANOG<sup>155,156</sup>, which are now used as diagnostic markers for germ cell neoplasia in situ by many pathology laboratories<sup>157</sup> (FIG. 7).

A hypothesis of a human testicular dysgenesis syndrome arose from these and other studies in the late 1990s<sup>85,140,158</sup> (FIG. 8). The hypothesis suggests that the syndrome is caused by maldevelopment of the fetal testis resulting in one or more of the following symptoms: germ cell cancer, low testosterone levels, undescended testis, hypospadias and impaired spermatogenesis. An important confirmatory observation was that several genetic mutations involving the differentiation and maturation of the male gonad can induce symptoms of testicular dysgenesis syndrome, sometimes all symptoms, including testicular cancer<sup>159</sup>. However, in most patients

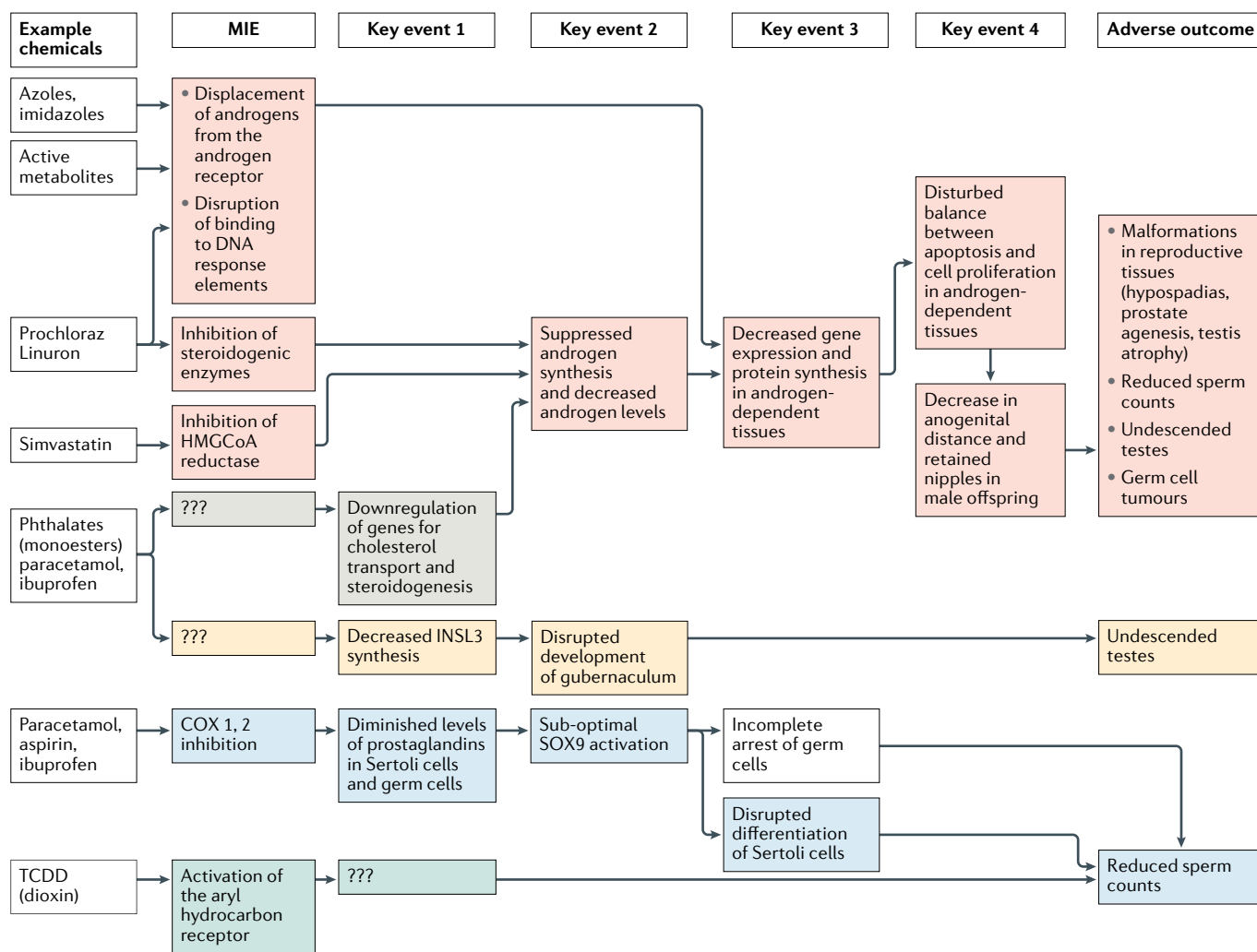
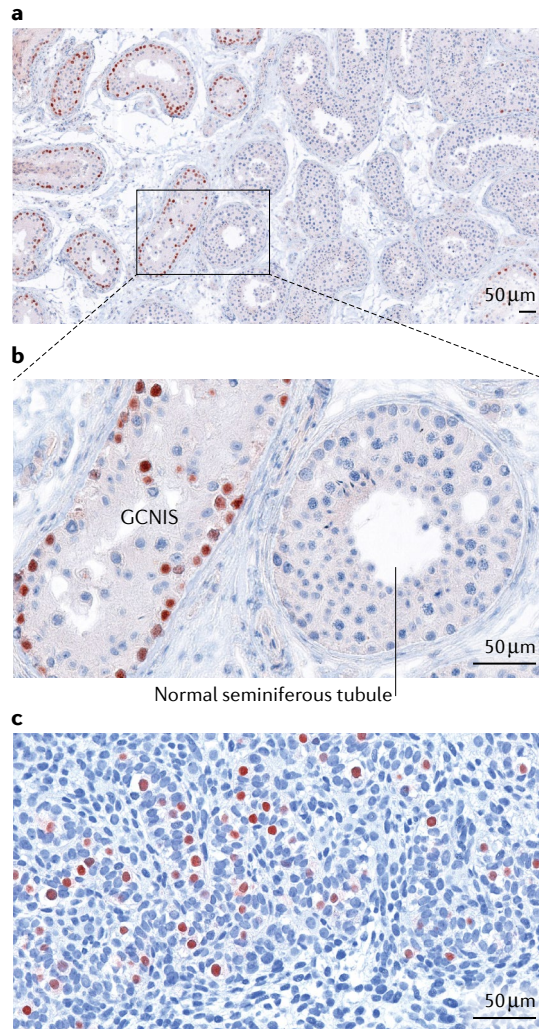


Fig. 6 | **Adverse outcome pathway network for the induction of male reproductive malformations.** Red cells depict pathways for androgen receptor antagonism and downregulation of steroidogenic enzymes, grey cells are for phthalate-mediated events, yellow cells are for the insulin-like peptide 3-mediated pathway leading to cryptorchidism, and blue cells highlight the prostaglandin-mediated pathways. Green cells are for the

dioxin-induced pathway leading to poor sperm counts. The adverse outcome pathway network is based primarily on observations in animal models<sup>142,212</sup>. COX, cyclooxygenase; HMGCoA, hydroxymethylglutaryl-CoA; INSL3, insulin-like peptide 3; MIE, molecular initiating event; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Figure adapted with permission from REF.<sup>141</sup>, Elsevier.



**Fig. 7 | Expression of the embryonic marker OCT4 in adult germ cell neoplasia in situ is similar to expression in germ cells (gonocytes) in normal fetal gonads.** **a** | Testicular tissue from an adult man with germ cell neoplasia in situ (GCNIS) expressing the embryonic marker OCT4 (red in immunohistochemical reaction). **b** | Box outlined in part **a** at higher magnification. This image shows GCNIS and a normal seminiferous tubule. **c** | For comparison, this image shows a healthy human fetal testis at gestational week 14 (from an induced legal abortion), with the same immunohistochemical staining for OCT4. Note the similarity between phenotypes of the normal gonocytes expressing OCT4 (red nuclei, embedded in fetal Sertoli cells) and the GCNIS cells in part **b**.

with testicular dysgenesis syndrome symptoms, no genetic alterations have been found and environmental exposures are likely to be involved<sup>131</sup>.

The links between testicular cancer, undescended testis, semen quality, decreased fertility and lower testosterone levels exist both at the individual and the population levels. In particular, the association between congenital undescended testis and increased risk of developing testicular cancer in adulthood is quite strong, at both the individual level<sup>160–162</sup> and the population level<sup>163,164</sup>. There is also good evidence that poor semen quality, decreased testosterone levels and

testicular cancer are linked<sup>165–168</sup>. In Denmark, the incidence (total number of new cases divided by the population at risk) of testicular cancer among men from the 1940s to 2010 increased by approximately 300% and has levelled off since 2000; however, levels are still among the highest in the world<sup>87</sup>. Also noteworthy is that there is evidence of a significant drop in average sperm counts among Danish and other European men since the 1940s<sup>79</sup>. In addition, a secular decline in testosterone levels has been observed, although changes in lifestyle factors, such as increased BMI, also seem to have a role in these trends<sup>169,170</sup>. Taken together, there seems to be little doubt that environmental effects are behind the trends in testicular cancer; however, the specific exposures remain to be determined.

### Role of modern lifestyles

#### Smoking

Tobacco smoking in young men has negative effects on their semen quality, as demonstrated in a large meta-analysis<sup>171</sup>. However, several studies suggest that maternal smoking during pregnancy is a stronger predictor of poor semen quality than the men's own smoking in adulthood<sup>178,172,173</sup>. There is also evidence that female smokers have lower fecundability than non-smokers, and a similar trend has been seen for male smokers in relation to fecundability<sup>174–177</sup>. In addition, e-cigarette use has been linked to impaired semen quality<sup>178</sup>; however, little is known about the impact of e-cigarette use in relation to fertility outcomes. The impact of marijuana smoking has been investigated, but with conflicting results<sup>178–180</sup>.

#### Alcohol

Another prevalent lifestyle factor that is widely debated in relation to reproduction is alcohol consumption. A follow-up study of 430 Danish couples trying to conceive showed that the odds ratio of conceiving decreased with increasing alcohol intake among women, with no clear pattern between alcohol intake in men and time to pregnancy<sup>181</sup>. However, a meta-analysis from 2016 that included 15 studies and more than 16,000 men found that alcohol intake was adversely associated with semen volume and morphology whereas no effects were seen in relation to sperm concentration and motility<sup>182</sup>.

#### Diet

In some studies, adherence to healthy dietary patterns has been positively associated with semen quality. These diets are typically characterized by food groups such as vegetables, fruits, nuts, whole cereals, seafood, poultry and low-fat dairy products<sup>183,184</sup>. In women, reduced intakes of fruit and increased intakes of fast food in the pre-conception period have been associated with infertility and modest increases in time to pregnancy<sup>185</sup>. The odds of infertility have been reported to be two to three times higher in US women who consumed meals not prepared at home (including fast food and ready-to-eat foods) than in those who did not<sup>186</sup>. Interestingly, both the male and female partner's intake of sugar-sweetened beverages has been adversely associated with couple fecundity (assessed as time to pregnancy)<sup>187</sup>.



### Obesity

Overweight is well established as a risk factor for reduced reproductive function in both sexes, and for fertility treatment in most public health services there are restrictions regarding access based on upper BMI limits for female individuals<sup>188</sup>. A review of 49 studies concluded that following ART, women with overweight or obesity had a lower live birth rate than women with a BMI in the normal range<sup>188</sup>. Fecundity of men might also be hampered by obesity<sup>189</sup>. Regarding semen quality, the overall conclusion from a meta-analysis including more than 13,000 men from the general population and men attending fertility clinics was that there is a U-shaped association between BMI and semen quality with both underweight and overweight being associated with an increased risk of oligospermia or azoospermia<sup>190</sup>. That both underweight and overweight were associated with reduced semen quality has been confirmed in a study of almost 4,000 sperm donors with repeated semen sampling<sup>191</sup>.

### Physical activity

Interestingly, increased levels of physical activity (within a moderate range) might, independent of obesity, be beneficial for semen quality<sup>192–195</sup>. In line with these observations, a randomized controlled trial of 419 infertile men showed that patients randomized to moderate aerobic exercise over 24 weeks had improved semen quality<sup>196</sup>.

### Industrialization

The industrial revolution, which was beginning around 1800 and accelerating from the mid-1800s, was based on the exploitation and consumption of fossil fuels, first coal and later also oil and gas. The increase in the use of fossil fuels was fairly modest in the 1800s<sup>197</sup>. However, during the late 1900s and the 2000s the world consumption of fossil fuels increased exponentially<sup>197</sup>. It is noteworthy that fossil fuels are not only energy sources, but they are also the basic raw materials for the production of more than 100,000 synthetic chemicals used in modern materials, such as plastics<sup>198</sup>, pesticides, pharmaceutical products, cosmetics, furniture, clothing, cars, aeroplanes

and numerous other modern products. According to the US Energy Information Administration<sup>199</sup>, approximately 7% of fossil fuels are consumed for non-combustion use in the USA. In China, which has become one of the main producers of chemicals for feedstocks for industry<sup>200</sup>, the percentage might be even higher. The environmental effects of usage of fossil fuels are, therefore, not only increasing CO<sub>2</sub> levels and effects on climate, but also increasing exposures of humans to mixtures of thousands of chemicals<sup>19,201–205</sup>.

There are several major sources of exposure to potentially harmful chemicals, including, combustion of coal, oil and gas products when used as energy sources in houses, cars, trains and aeroplanes<sup>206,207</sup>. There is also direct contamination of chemicals released from consumer products made from fossil fuels, such as plastics, textiles, building materials, cars, food additives, food packaging materials, pesticides, cosmetics and pharmaceuticals. In addition to indirect contamination via an environment polluted with rubbish containing these materials, where chemicals leak into the air, rivers, lakes and seas they might eventually end up in drinking water and our diet, including dairy products, meat and fish<sup>17</sup>. And, finally, exposures can occur from fossil fuel production sites (such as fracking<sup>208</sup>) or oil spill accidents<sup>209</sup>.

However, except for disasters with major leakage of chemicals (such as the Seveso disaster in Italy in 1976)<sup>210</sup>, the precise origins of chemicals present in human tissues are generally not known<sup>204,211</sup>. Numerous potentially harmful chemicals have been found in samples of blood, urine, semen, placenta and breast milk of all humans investigated<sup>17</sup>. They have also been demonstrated in human adipose tissues, such as the persistent chemicals dioxins, polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT) and flame retardants<sup>17</sup>. Other chemicals (such as phthalates, bisphenols, perfluorinated compounds (PFCs), pesticides and some UV filters), including those that originate from the use of plastics, building materials, food, food packaging, cosmetics, sunscreens and drinking water, belong to the so-called non-persistent chemicals, which are excreted from the body within hours<sup>17</sup>. It is noteworthy that many of these chemicals have endocrine-disrupting properties

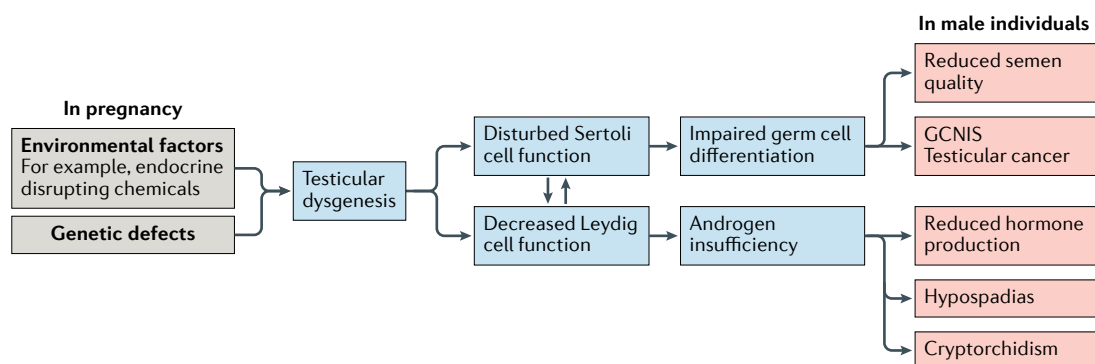


Fig. 8 | **Testicular dysgenesis syndrome.** The hypothesis shown here links fetal maldevelopment of the male gonads to congenital malformations visible at birth and late-onset symptoms occurring in adulthood, including GCNIS (germ cell neoplasia in situ) that develops into germ cell cancer (seminoma and non-seminoma), and/or infertility and/or decreased testosterone production<sup>95</sup>. Some patients with testicular dysgenesis syndrome have all symptoms, others only one or two.



and have been shown to interfere with reproduction in non-human animals, both in laboratory settings and wild animals, including some that are threatened species<sup>19,212,213</sup>. The literature on human effects is, however, sparse. Nevertheless, an analysis of the burden of endocrine disruptors for male reproductive health estimated that endocrine-disrupting chemicals might contribute substantially to male reproductive disorders and diseases, with an associated annual cost of nearly €15 billion in the EU alone<sup>214</sup>.

Although the development towards more fossil fuel-based industrialization has been increasing during the past 150 years, this trend was interrupted in Denmark during World War I and World War II (Supplementary Fig. 8). Interestingly, the ‘testicular cancer risk curve’ for birth cohorts of men born in Denmark during World War II mirrors the curve for import of fossil fuels (Supplementary Fig. 8) in line with evidence that this cancer has a fetal origin from embryonic germ cells<sup>215</sup> (FIG. 7). It is also noteworthy that the fertility rate changed during World War I and World War II<sup>8</sup> (FIG. 2).

**A research challenge**

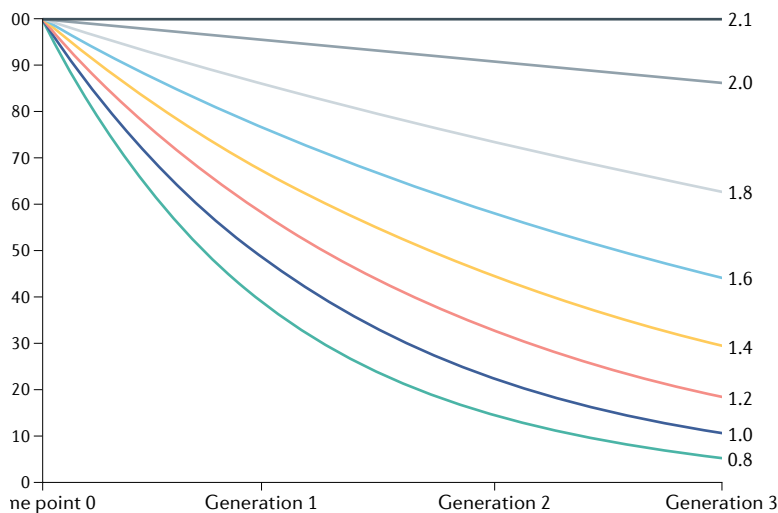
The difficulty in distinguishing between the biological or behavioural factors, including educational attainment<sup>1</sup>, that affect human fertility has led researchers to conclude that the question on the causality underlying the decline in human fertility cannot be answered<sup>216</sup>. The essence of the problem is that behavioural factors (which are influenced by social and cultural factors, for instance) can modulate the effects of biological factors causing misleading conclusions<sup>216</sup>. This problem is further complicated by the fact that fertility involves gametes from two individuals, and that the success thus depends on both individuals. To understand the complex scenario of human fertility and its deterioration

since the start of industrialization, a multidisciplinary perspective is needed involving disciplines capable of producing evidence on both the behavioural and the biological components.

The most important measurable biological factor acting on fertility is fecundity. Fecundity is the result of our genes and the environment interacting with these genes (that is, how genes are expressed in different environments). An approach for understanding the biological component of the declining fertility is thus to understand how genes and environment influence fecundity. Individual fecundity depends on several individual phenotypes: the quality of gametogenesis, migration of the spermatozoa to the oocyte, fertilization, implantation and survival of the conceptus. Measures of couples’ fecundity have most often been estimated using a pregnancy-based approach, in which waiting time to pregnancy (the number of months of unprotected intercourse before conception) is retrospectively assessed among couples who eventually have a proven pregnancy<sup>217</sup>. A twin study found that the causal genetic component for time to pregnancy differs by sex (6% for men and 30% for women) but that most of the causal variation is explained by environmental factors<sup>218</sup>.

To truly understand couples’ fecundity, it is thus essential to focus on the environmental factors acting throughout the lives of the individuals. Unfortunately, time to pregnancy is a biased measure of the true fecundity as it excludes couples who do not become pregnant, thus leading to an overestimate. A better measure of true fecundity is the prospective cohort approach, which does not have this limitation because couples are recruited before they start unprotected intercourse and are then followed to monitor the occurrence of a pregnancy<sup>219</sup>. However, studies suggest that a high proportion of pregnancies are unplanned<sup>23</sup> and they might not be included in prospective time to pregnancy studies, which could bias the results, as such couples might be more fecund than couples planning a pregnancy<sup>220</sup>. Thus, study findings cannot be directly extrapolated to the general population. Another approach is to include unsuccessful attempts to become pregnant retrospectively. However, the quality of recall of the occurrence and duration of such unsuccessful attempts to become pregnant has not been assessed and might be poor<sup>220</sup>. Because of the drawbacks of the above-mentioned approaches, the so-called current duration designs have been suggested<sup>221</sup> in which retrospective information about current attempts is obtained thereby making it possible to include unsuccessful attempts and unplanned pregnancies<sup>221</sup>. This method thus offers the possibility to examine the first step for understanding the biological causal component for our decreasing fertility, namely the fecundity in our populations.

The inclusion of a population sample of people of common reproductive ages (for example, women aged 18–45 years and men aged 18–55 years) is essential for a population-based approach to assessing fecundity. Within this sample, it is important to understand the observed patterns found for the individual couple’s fecundity, thus separately examining the male and female components. For instance, semen analysis and



**Fig. 9 | Levels of unsustainable fertility rates and population sizes (newborn babies) over three generations.** A population is sustained if the total fertility rate is 2.1 (total fertility rate is the average number of children per woman). Almost all industrialized regions have rates below that level. If the current unsustainable rates persist, considerable demographic changes will occur within one to three generations (excluding migration), resulting in ageing societies followed by population decline, shown here as percentage declines in the number of newborn babies.

## Box 1 | Transdisciplinary research needed

Broad collaboration between researchers in life sciences and social sciences, including anthropology and demography, is needed to answer important questions.

- How can we establish methods to distinguish between voluntary and non-voluntary childlessness in populations with unsustainable reproduction?
- How can we develop new methods to distinguish between the role of male and female factors in couple fecundity?
- Can we identify novel biomarkers in early life that predict the adult reproductive capacity of an individual?
- What are the biological mechanisms that link testicular cancer to poor spermatogenesis and other reproductive disorders in young men?
- Why are there multiple reports on adverse trends in male reproductive health, but not similar reports on female reproduction?
- Is it possible that exposures to industrial endocrine-disrupting chemicals are more harmful for the male than the female reproductive organs, due to the anti-androgenic and oestrogenic properties of many of these chemicals?
- Why is human spermatogenesis much poorer than spermatogenesis of most other mammals?
- Why have serum levels of testosterone in human males declined during the past generation? Is it due to environmental exposures or does the obesity epidemic have a role as well?
- What can we learn from scientists studying reproduction of endangered wildlife species?
- Is it possible that human fertility rates will return to sustainable levels in countries/regions where they have been below sustainable levels for decades?

variation by environmental exposures, as well as analyses of reproductive hormones and environmental chemicals, will help identify fecundity biomarkers. Equally important is obtaining information on the environmental exposures (such as lifestyle and the working environment) that might influence fecundity in the couples. The current duration design offers a direct possibility for doing so, which has been illustrated by the fact that tobacco smoking in women is associated with a doubling in the median duration of unprotected intercourse before pregnancy<sup>221</sup>. The feasibility of the current duration design has further been demonstrated as information on fecundity was obtained without significant selection bias<sup>222</sup>, which suggests that this design is a strong basis for further understanding of fertility problems. However, to get an understanding of the fertility changes in the population, we also need data on behavioural factors, such as voluntary and involuntary childlessness and the complex economic, social and educational profiles of couples currently attempting to conceive. We also need to describe pregnancy planners and non-planners, and changes in planning behaviour over time. The determinants controlling these behavioural factors are manifold, and include changes in an individual's identity in connection with childbearing and raising children. It is thus only multidisciplinary studies that can help us understand the reasons behind the ongoing decrease in fertility rates.

## Conclusions

A crucial problem is that knowledge about the causes underlying the global downturn in births is not available. The trend was already visible in Denmark around 1900, when fossil fuel-based industrialization had just started, and occurred without the use of modern contraception, which was introduced half a century later. It remains to be elucidated whether the decreasing fertility rates are linked to changes in our biological systems due to environmental exposures or to behavioural socioeconomic changes caused by modern lifestyles, or due to a combination of both.

In support of a biological hypothesis, the trends in testicular cancer that can be seen as the 'canary in the coal mine' for other spermatogenic disorders, are clearly increasing. In addition, infertility due to poor semen quality is widespread and the need for MAR, and use of ICSI for male infertility, has become a costly issue and a booming health industry in many parts of the world.

Also in favour of a biological hypothesis is the fact that reproductive toxicants are ubiquitously present in our diet, drinking water and the air we breathe<sup>17</sup>. It is well established that these chemicals have become part of our tissues and fluids. But do they contribute to the current epidemic of infertility? We know that they can be a threat to wildlife. Unfortunately, too little has been done to uncover their role in humans.

For many societies in Asia and Europe, the population situation is now rather dire. Countries/regions with a rate of 1.5 children per woman (such as Japan and Germany) have already seen a 50% reduction in the number of babies born, and will (excluding migration) face a further 50% reduction over the next 60 years if current trends in fertility rates persist<sup>1</sup> (FIG. 9). South Korea, with a fertility rate in 2020 of 0.84 will (excluding migration) experience a 75% reduction in the number of babies born within the next two generations, if current birth rates persist<sup>223</sup>.

We urge governments, health authorities, including WHO, and universities to seriously address the prospects for human reproduction. If further analysis should show that the reproductive trends can be explained by socioeconomic and psychological factors alone, we might not need to worry so much, as economic and social factors often change. However, the trends seem to have developed slowly over more than a century during economic upturns and downturns. If the fertility problems are, at least partly, due to anthropogenic activities that are causing increased environmental exposure to harmful chemicals, in addition to effects on climate, decisive regulatory actions underpinned by unconventional, interdisciplinary research collaborations will be needed to reverse the trends (BOX 1).

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#### Author contributions

N.E.S., R.L.-J., A.-M.A., S.A.H., E.V.B., K.A., L.R.F., A.Z., R.J.H. and A.J. researched data for the article, contributed substantially to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission. H.L., N.J., K.M.M., Ø.L. and A.K. contributed substantially to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission. L.P. researched data for the article, contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission.

#### Competing interests

R.J.H. is the Medical Director of Fertility Specialists of Western Australia and has equity interests in Western IVF. The other authors declare no competing interests.

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