Dietary trends and the decline in male reproductive health

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Abstract

Over the 20th century, male reproductive health has suffered a substantial decline, as evidenced by decreases in sperm counts and testosterone levels and increases in reproductive pathologies. At the same time, the prevalence of chronic diseases such as obesity, diabetes, and metabolic syndrome has risen dramatically. Metabolic and reproductive health are highly interconnected, suggesting that their respective trends are intertwined and, given the timeframe of such trends, environmental and not genetic factors are most likely to be the primary causes. Industrialization, which began in Europe in the mid-18th century, has resulted in profound changes to our diet, lifestyle, and environment, many of which are causal factors in the rise in chronic diseases. Industrialization results in a nutrition transition from an agricultural unprocessed to a modern processed diet, incorporating increases in sugar, vegetable oils, ultra-processed foods, linoleic acid, trans-fats, and total energy. This dietary shift has incurred numerous adverse effects on metabolic and reproductive health, characterized by chronic inflammation, oxidative stress, and insulin resistance. Moreover, these effects appear to multiply across subsequent generations via epigenetic inheritance. Men's fertility is markedly affected by obesity and diabetes, with an increase in total energy via processed food intake arguably being the key factor driving the diabesity pandemic. In contrast, wholefoods rich in micronutrients and phytonutrients support male fertility and a healthy body weight. Therefore, men wanting to maximize their fertility should consider making positive dietary changes, such as replacing processed foods with unprocessed foods that support metabolic and reproductive health.

Keywords: Fertility, Diet, Reproductive health, Testosterone, Sperm, Semen

Abbreviations: EDC, endocrine-disrupting chemical**;** MRH, male reproductive health; MUFA, monounsaturated fatty acid; NC, not calculated; OR, odds ratio; PUFA, polyunsaturated fatty acid; T2D, type 2 diabetes; TFAs, trans-fatty acids; RCT, randomized controlled trial; SFA, saturated fatty acid; TDS, testicular dysgenesis syndrome; TT, total testosterone; UPF, ultra-processed food

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1. Introduction

Several lines of evidence point to a worldwide secular decline in male reproductive health (MRH) over the 20th century and continuing today in the 21st century, namely, decreases in sperm counts and testosterone and increases in cryptorchidism, hypospadias, and testicular cancer. These trends share many epidemiological and experimental links, suggesting that such trends are not distinct but interconnected [1]. This has led previous authors to propose a unified theory called testicular dysgenesis syndrome (TDS), which claims that such trends share a common etiology and, given the timeframe of these trends, are driven largely by environmental factors [1, 2]. It has been argued that the decline in MRH is a causative factor in declining fertility rates worldwide [3]. It has been suggested that exposure to endocrine-disrupting chemicals (EDCs) in fetal and early life constitutes a major environmental cause of TDS [1, 2]. Both cryptorchidism and hypospadias increase the risk of testicular cancer [4], which typically has a peak incidence at 25-45 years [5], indicating that TDS has its origin in early life [1]. However, poor semen parameters and testosterone levels can be improved via dietary changes in later life [6–8], implying that etiological factors for the wider secular decline in MRH may be either distinct or similar but of a different duration, intensity, or timing of exposure.

The industrial revolution, which began in Britain in the mid-18th century and later spread elsewhere [9], has caused profound changes to our environment and lifestyle, including changes in diet, physical activity, sleep, psychological stress, and toxin exposure [3, 10–13]. Moreover, increasing industrialization and modernization over the 20th century has led to further changes in these areas. For example, the shift from agricultural to factory work and then later to office work has led to a progressive decline in work-related physical activity [10]. Such changes bring humans further away from the environment in which the majority of our evolution took place. The genus *Homo* has spent 99.5% of its history as hunter-gatherers, 0.5% as farmers, and 0.01% in the post-industrial era [14]. Although some genetic adaptation took place after the Neolithic revolution, it is unlikely that much has taken place in the industrial age [14]. This gives rise to a mismatch between our genes and environment causing adverse effects, many of which drive the rise in chronic diseases, also called diseases of civilization, a concept termed evolutionary mismatch [15, 16].

Previously, industrialization was predominantly linked to the decline in MRH via increased exposure to EDCs [3]. However, the substantial changes in other environmental factors and their links with MRH warrant further investigation. Post-industrial dietary changes have had a significant impact on human health and are strongly linked to the 20th century rise in chronic diseases, such as obesity, diabetes, and metabolic syndrome [17–19]. Metabolic and reproductive health share many epidemiological and experimental links, suggesting that their respective trends are interconnected. Thus, the present review argues that the secular decline in MRH may be viewed as part of the wider rise in chronic diseases over the 20th century, driven largely by post-industrial environmental changes, resulting in evolutionary mismatch. The review focuses on post-industrial changes in diet and their contribution to the decline in MRH, although other environmental factors have undoubtably contributed as well. Previous reviews have not considered data on dietary trends [20, 21]; thus, the impact of diet on the decline in MRH remains ill-defined. This work therefore uses observational, experimental, mechanistic, and dietary trends data to provide a more complete account of the impact of post-industrial dietary changes on MRH.

2. Trends in MRH

Semen parameters and reproductive hormones offer easily measurable biomarkers which, due to long-term usage, enable temporal trends in MRH to be examined. Reproductive pathologies offer another avenue for temporal trend assessment, although due to their relatively low incidence these may be less reliable.

2.1. Sperm

Four meta-analyses have found there to be a secular decline globally in sperm concentration, with estimates ranging from -0.87 to -0.95 million/ml/year, or -0.8 to -1.04% /year (Fig. 1a) [22–25]. In addition, secular declines have been observed in semen volume (-0.13 ml/year) [22] and total sperm count (-2.06 million/year) [25]. Individual studies and subregional meta-analyses across the world have reported consistent declines in normal morphology and inconsistent declines in motility [26–31]. The studies included in these analyses took place between 1931 and 2018; however, only 16 studies are pre-1970, whereas over 200 studies are post-1970. For sperm concentration, meta-analyses adjusted by geographical region show similar rates of decline across regions (Fig. 1b) [24], although when also adjusted for confounding variables, including selection bias, western countries show a steeper decline than non-western countries (-1.27 vs -0.65 million/ml/year) (Fig. 1c) [25]. This difference may be due to regional differences in genetic or environmental factors, such as differing levels of industrialization [3]. Interestingly, a recent study found that infertile men in the US (highly-industrialized) vs Iraq (developing country) had age-matched, lower sperm concentration (-29.85 million/ml), total count (-127.3 million), and motility (-10.3%)[1] [32], indicating that the level of industrialization is an explanatory factor in geographical declines. Additionally, the latest meta-analysis determined that studies post-2000 vs post-1972 showed a steeper decline in global sperm concentration (-1.73 vs -1.17 million/ml/year) and total count (-5.26 vs -4.7 million/year), suggesting that these declines may be accelerating [25].

2.2. Testosterone

Nine studies have reported a secular decline in total testosterone (TT) beginning in the 1970s (Table 1), with age-adjusted estimates ranging from -0.6 to -1.6%/year [33–35]. Additionally, two studies have noted an increase in hypogonadism or low T prevalence (Table 1), the largest of which found that between 2008 and 2017, US hypogonadism prevalence increased from 0.78% to 5.44% [36]. Four out of five studies have observed secular declines in bioavailable or free testosterone (Table 1), with age-adjusted estimates for bioavailable testosterone -1.4% /year [33] and free testosterone -0.5% /year [35]. The increase in BMI over the 20th century appears to account for a proportion of the overall trend of declining testosterone levels, but likely no more than ~50% [37]. Although not as well-established as the decline in sperm counts, the decline in testosterone also seems to be global as the current evidence covers industrialized countries in North America, South America, Europe, and Asia. High levels of testosterone in the testis are essential for spermatogenesis [38], and several studies in sub- and infertile men have associated low testosterone with impaired fertility and poor semen parameters [39–42]. The largest of these studies (n = 5177) found that the prevalence of hypogonadism in men with low total sperm counts (<39 million) was 45% [42]. Within the general population, testosterone and semen parameters may not directly correlate, unlike other markers of Leydig cell dysfunction which do, such as increased luteinizing hormone [43]. Overall, this evidence suggests that the temporal trends in semen parameters and testosterone are interconnected.

[1] Throughout the text, sperm motility and morphology percentages refer to absolute units, not proportional differences.

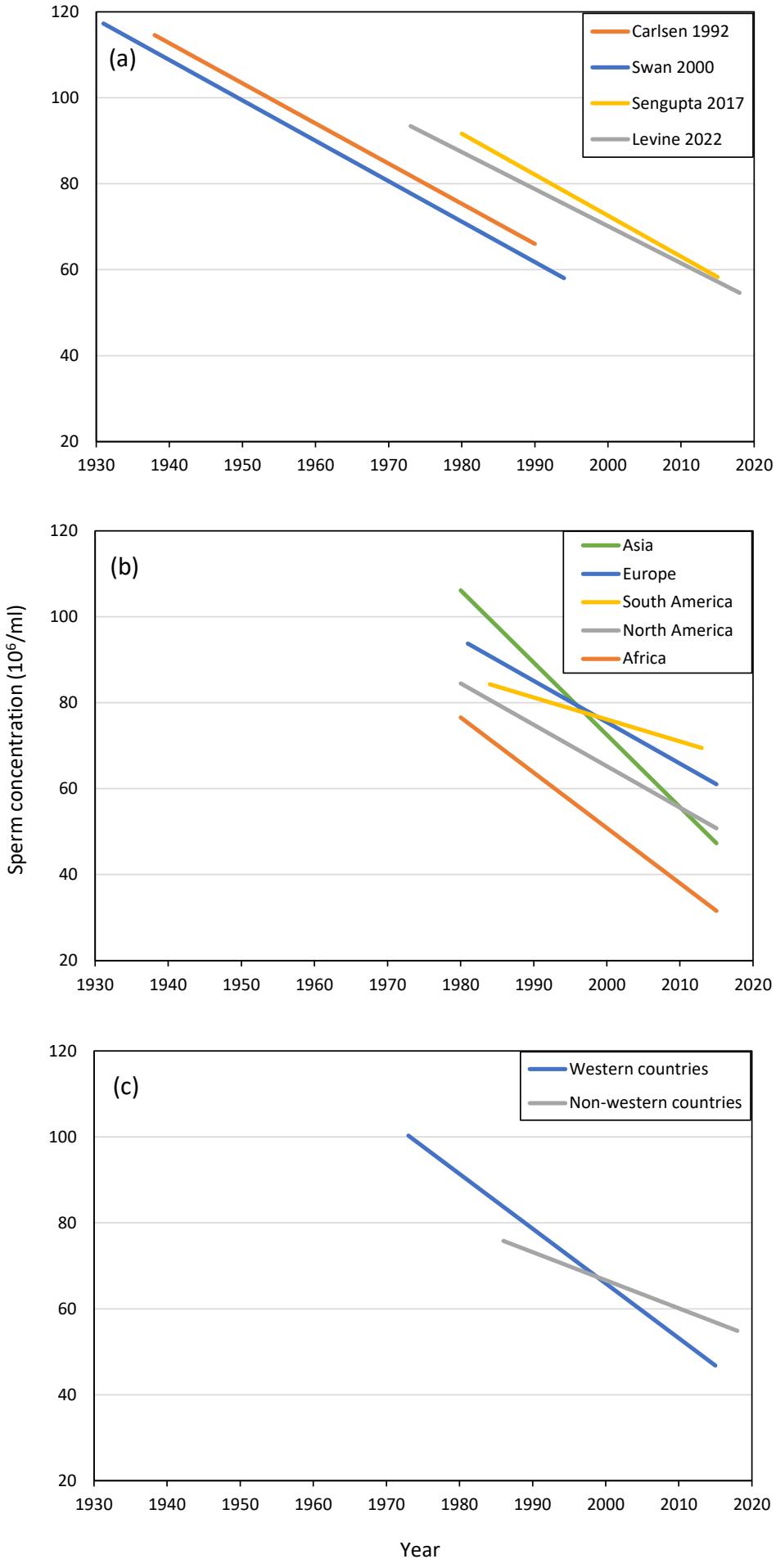

Fig. 1 The decline in sperm concentration over time. Significant decreases in all estimates ($p < 0.05$), excepting South America. A: world, linear regressions, weighted (1931-2018); data from different meta-analyses [22–25]. B: geographical regions, linear regressions, unweighted (1980-2015); data from Sengupta 2017 [24]. C: geographical regions, meta-regressions adjusted for confounding variables: age, abstinence time, collection methods, selection bias, and statistical considerations (1973-2018). Western countries: North America, Europe, Australia, New Zealand. Non-western countries: Africa, Asia, South America. Data from Levine 2022 [25]

Table 1 Studies showing a secular decline in testosterone

Study	Location	Years covered	Sample size	Significant age-adjusted decline in TT	Significant multivariate-adjusted decline in TT	Significant age-adjusted decline in free or bioavailable testosterone	Significant multivariate-adjusted decline in free or bioavailable testosterone	Adjusted variables
Travison 2007 [33]	USA	1987-2004	1532	Yes	Yes	Yes	Yes	BMI, smoking, comorbidities, general health, medications, employment, marital status
Nyante 2012 [35]	USA	1988-2004	2315	Yes	No	Yes	No	BMI, smoking, alcohol, waist circumference
Mazur 2013 [37]	USA	1982-2002	991	Yes	Yes	NC	NC	BMI
Walsh 2015 [44]	USA	2002-2011	44,762	Yes[a]	NC	NC	NC	None
Lokeshwar 2021 [45]	USA	1999-2016	4045	Yes	Yes	NC	NC	BMI, smoking, alcohol, comorbidities, physical activity
Auerbach 2021 [36]	USA	2008-2017	173,756,811	Yes[a]	NC	NC	NC	None
Andersson 2007 [46]	Denmark	1982-2001	5350	Yes	No	No	No	BMI
Trimpou 2012 [47]	Sweden	1995-2008	151	Yes[b]	Yes[b]	Yes	NC	Body weight
Perheentupa 2013 [48]	Finland	1972-2002	3271	Yes	Yes	Yes	Yes	BMI
Laranja 2020 [34]	Brazil	2010-2017	2874	Yes	NC	NC	NC	None
Chodick 2020 [49]	Israel	2006-2019	102,334	Yes	NC	NC	NC	None[c]

Table adapted and expanded from Chodick, 2020 [49]. Abbreviations: NC, not calculated. TT, total testosterone.

[a] Increase in hypogonadism or low testosterone prevalence

[b] Significant only in men 55-64 years: non-significant declines in those 35-54 years, likely lack due to small sample size and lack of statistical power. Body weight adjusted analyses only performed for 55-64 years, other age groups showed no significant change in body weight.

[c] No significant change in BMI over study period

2.3. Reproductive pathologies

There has been a global increase in testicular cancer incidence since the 1970s, most notably in Europe and North America, although countries in Latin America and Asia also show increases, albeit smaller and less consistent [3]. In countries that industrialized early, such as the UK and US, which have data starting sooner, testicular cancer mortality is seen to have been on the increase as from 1911 and 1933, respectively [50]. Moreover, although not completely uniform, the evidence base suggests that the incidence of cryptorchidism and hypospadias increased from the mid-1960s in Europe and North America [51, 52], and in some countries in Asia and Latin America, appearing to coincide with increasing industrialization [51, 53, 54]. In addition, a Danish study (1998-2017) found that the incidence of gynecomastia increased from 5 to >10-fold in adolescent and adult men, depending on the age group [55], although data for other countries are sparse. Gynecomastia is typically due to excess estrogens and/or androgen deficiency [56], indicating a secular change in male sex hormones. A large observational study covering 32 countries found positive correlations between the rates of hypospadias, cryptorchidism, and testicular cancer, and a strong negative correlation between testicular cancer and population sperm concentrations ($\rho = -0.88$) [57], helping to establish a link between secular increases in reproductive pathologies and declines in semen parameters.

2.4. Fertility

It is notable that the adverse trends in MRH start when the data begin and are thus likely to have begun before. Fertility rate data go back further and, while such data are affected by numerous variables, they offer an insight into fecundity trends, both male and female. In Western Europe in the late-19th century, there was a clear decline in fertility rates from ~5 to 2 births per woman (Fig. 2a), which coincided with rapid industrialization [58]. Furthermore, worldwide data from 1950 show that fertility rates and declines are stratified by the level of industrialization, as measured by either income level or geographical region, for instance, Europe vs Sub-Saharan Africa (Fig. 2c and d) [9]. Industrialization affects a number of variables linked to fertility rates [59], but ultimately these boil down to either less intercourse, increased *coitus interruptus*, increased artificial contraception, or reduced fecundity. The first two explanations rely on individuals en masse making different choices due to changes in cultural or socioeconomic circumstances on which there is a lack of consensus [59, 60]. Artificial contraception likely explains a proportion of these trends, as the late-19th century saw a rise in condom use [61], while from the 1960s onwards, increased use of contraceptive pills is observed [62]. However, industrialized countries which legally prohibited artificial contraception and abortion for periods of time (e.g., Ireland and France) [63–67] do not show reversals of fertility rates back to pre-industrial levels and are largely comparable to countries with relatively few restrictions (UK) (Fig. 2b) [68, 69].

Twin births may be viewed as a marker of fecundity, as they require double-fertilization. Industrialized countries show a decrease in twinning rates (~25%) from the early to mid-20th century, depending on the country, to a nadir around 1980, which persists in maternal age-specific and age-standardized data (where available) [70–74]. Some countries with data starting earlier show a slight increase preceding this decrease (i.e., Sweden, Finland, Denmark, England, and Wales) [72–74], suggesting that environmental factors affecting fecundity may have initially improved, then worsened to a greater degree, for instance, an initial improvement in basic nutritional sufficiency, later outweighed by the increasing refinement of the diet (section 5). Interestingly, long-term Swedish data (1751-1960) show that county twinning rates converged over time to a common low rate around 1960, this appearing to be driven by increasing industrialization and urbanization [75]. Moreover, rural vs urban areas had higher twinning rates in Finland between 1860 and 1959 (~15%)

[76]; however, rates were comparable between such areas in Denmark from 1978-82 [77], indicating that by the late 20th century, environmental influences were similar between such areas.

Since their nadir around 1980, twinning rates have approximately doubled in industrialized countries largely due to medically assisted reproduction [71]. From 1997-2018, European births via assisted reproductive technologies rose from 35,314 to 215,610, i.e., over a six-fold increase, now accounting for 3.5% of total births [78]. Percentages of total births vary substantially across European countries, from 0.1% in Serbia to 9.3% in Spain [78]. On the other hand, these figures only account for births via assisted reproductive technologies and not from the broader category of medically assisted reproduction [79]. Assisted reproductive technologies plus intrauterine insemination accounted for 3.8% of European births in 2018, but this still does not include other techniques such as ovarian stimulation, which would likely make these trends more pronounced. Whether such trends are a sign of increased infertility is less clear, as they may represent greater population access to reproductive medicine by a stable subset of infertile couples. Nevertheless, when viewed together with the decrease in twinning rates and semen parameters, the increase in medically assisted reproduction is most probably due to increased infertility.

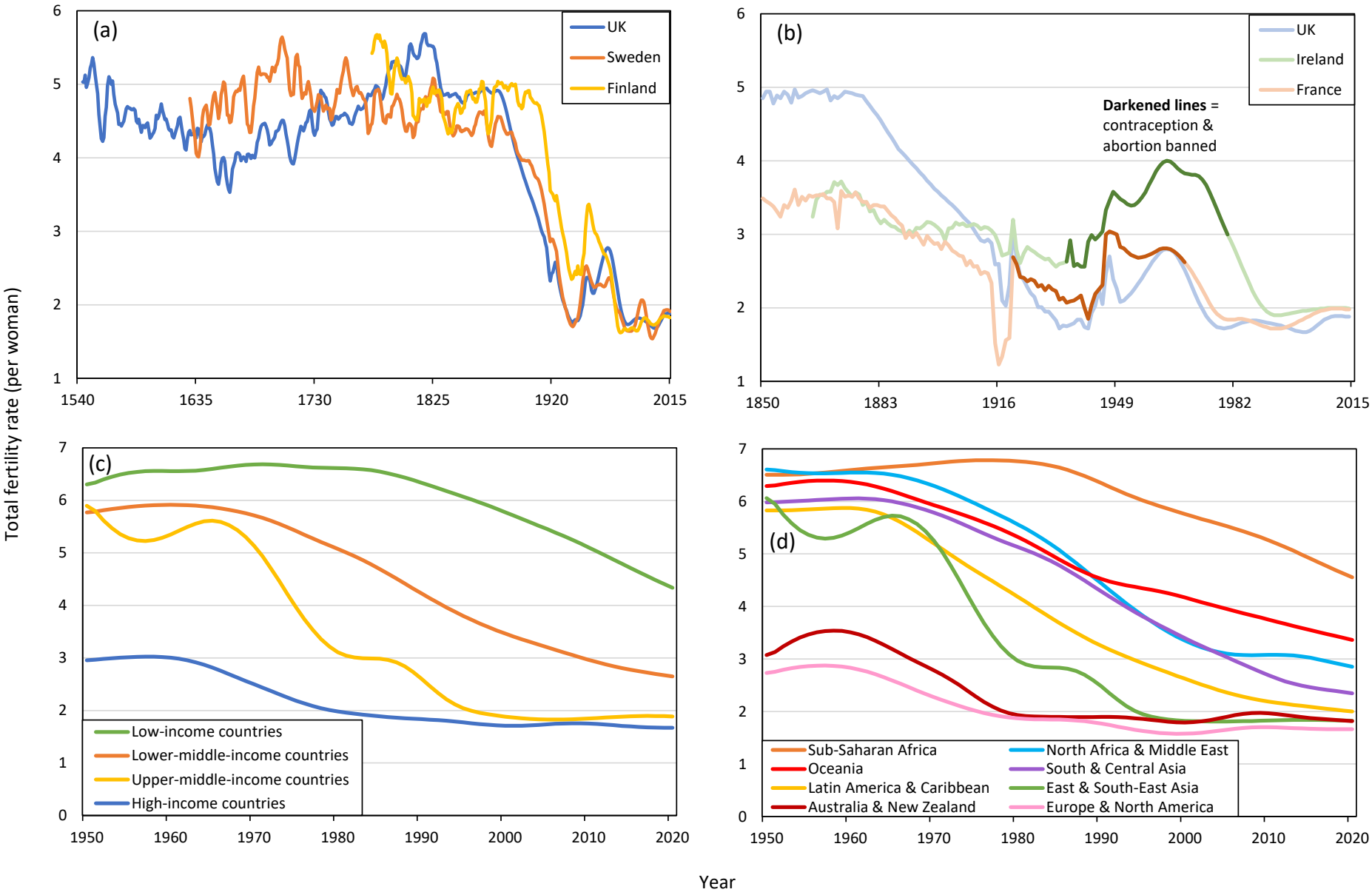

Fig. 2 The decline in fertility rates over time. Data for A and B from Gapminder version 6 (pre-1800) and version 12 (post-1800) [80, 81]. Data for C and D from United Nations [82]. A. Fertility rate in countries with long-term data, 5-year moving averages (1541-2014). B. Fertility rate in countries with periods of legally prohibited abortion and contraception (lines darkened to indicate these periods), compared to the UK with minimal restrictions (1850-2014). C. Fertility rates by country income group (1950-2020). D. Fertility rates by geographical region (1950-2020)

3. Trends in metabolic health

An examination of the prevalence rates of obesity, diabetes, and metabolic syndrome over the 20th century enables an in-depth assessment of temporal trends in metabolic health. The links between metabolic and reproductive health discussed below (section 4) highlight the importance of similarities between such trends.

3.1. Obesity

From 1975 to 2016, global adult male obesity prevalence rose from 3 to 11.6%, and mean BMI from 21.7 to 24.5 kg/m^2 [83]. Although obesity has increased in all regions worldwide since the 1970s, rates of increase and absolute prevalence differ substantially. This is due to many reasons, but two are of note here. Firstly, regions undergoing extensive industrialization and urbanization during the 20th century saw some of the largest increases in obesity, such as Latin America, Eastern Europe, and the Middle East, in contrast to regions with much slower rates of industrialization which saw smaller increases, such as Sub-Saharan Africa and South Asia (Supplementary Fig. 1) [9]. Moreover, in countries which underwent industrialization much earlier, such as the US, obesity prevalence can be seen to increase as early as in the 1890s [84], and the highest regional obesity prevalence continues to be in highly-industrialized western countries (Supplementary Fig. 1), highlighting the link between industrialization and obesity. Secondly, regions such as Oceania (excluding Australia and New Zealand) show large increases in obesity in contrast to more industrialized regions, such as the Asia Pacific high income region, which show only small increases (Supplementary Fig. 1). This may be due to differences in genetic predisposition to obesity [85, 86], as such areas are ethnically homogenous [87]. It appears that populations which have been insulated from industrialization and global trade the longest, such as the Pacific islands [88], are particularly susceptible to obesity when rapid modernization and urbanization take place due to thrifty genotypes [86], indicating greater evolutionary mismatch.

3.2. Diabetes and metabolic syndrome

Approximately 90% of people with type 2 diabetes (T2D) are overweight or obese [89], as obesity typically increases insulin resistance and deficiency [90]. From 1980 to 2014, global adult male diabetes prevalence rose from 4.3 to 9% [91], of which ~90% is T2D [92]. Geographical trends that reveal industrialization and genetic susceptibility again appear to be explanatory factors. Oceania had the largest increase in diabetes prevalence over this period (Supplementary Fig. 1), probably due to increased predisposition owing to high rates of obesity [89, 90] underpinned by greater evolutionary mismatch (section 3.1.). Similarly, regions with greater industrialization over the 20th century, such as the Middle East, Latin America, and the high-income Asia Pacific region, have higher diabetes prevalence than regions with less industrialization, such as Sub-Saharan Africa and South-East Asia (Supplementary Fig. 1) [9]. Where data exist, diabetes prevalence can be seen to have increased sooner in countries that industrialized early. For example, in the US, diabetes prevalence increased from the 1930s [93], reaching 0.9% in 1958 and steadily rising to 7.4% in 2015 [94]. Both diabetes and obesity were rare in pre-industrial populations and are considered diseases of civilization [95]. Additionally, the prevalence of metabolic syndrome has increased across various industrialized countries in recent decades [96–98], with a current global prevalence ~25-30% [96]. Metabolic syndrome is typically defined as a combination of obesity, insulin resistance, dyslipidemia, and hypertension [99]. Current global prevalence of male hypertension (30-79 years) is 34%, and trends show increases in developing countries and decreases in highly-industrialized countries [100]. Moreover, several studies in industrialized countries have noted a secular increase in triglycerides

[101–103]. Non-alcoholic fatty liver disease, which is strongly associated with metabolic syndrome, has also increased in recent decades, with a global prevalence of ~25% [104, 105].

4. Links between reproductive and metabolic health

The concurrent secular increases in metabolic dysfunction and poor MRH and the extensive literature on the links between metabolic and reproductive health suggest that their trends are intertwined.

4.1. Obesity and reproductive health

A 2021 systematic review of 60 observational studies found that overweight and obesity were associated with poorer semen parameters, lower TT, and higher estradiol [106]. Moreover, a 2013 meta-analysis reported a 9.8% body weight loss via diet increased TT by 2.87 nmol/L and 32% weight loss via bariatric surgery by 8.73 nmol/L [7], establishing a relationship between obesity and testosterone. Regarding a potential causal relationship between obesity and semen parameters, a systematic review of 90 bariatric surgery patients found a moderate increase in normal morphology, but no significant changes in sperm concentration or progressive motility, although this review included heterogenous study designs and a small sample [107]. A recent RCT (*n* = 47) observed that a 13.5% weight loss increased sperm concentration by 13.2 million/ml and total count by 59.4 million, while in participants who maintained the weight loss, improvements persisted for a year along with reduced C-reactive protein and Hb1Ac [108]. Furthermore, an observational study reported that weight loss significantly improved sperm DNA fragmentation and normal morphology [109], and a 2015 meta-analysis found that obese men had higher rates of infertility [odds ratio (OR) = 1.66] and reduced live births per assisted reproduction cycle (OR = 0.65) [110]. Mechanistically, obesity impairs MRH by inducing systemic inflammation and disrupting testicular steroidogenesis and the hypothalamic-pituitary-gonadal axis [111]. In contrast, there appears to be little association between obesity and testicular cancer [112], thus indicating a different etiology.

4.2. Diabetes, metabolic syndrome, and reproductive health

Meta-analyses have shown T2D patients to have lower TT than controls (-2.99 nmol/L) [113], and higher TT at baseline, which decreases the risk of developing T2D (relative risk = 0.65) [114]. Furthermore, a 2020 meta-analysis reported that testosterone replacement therapy in T2D and metabolic syndrome improved markers of insulin resistance [115], while a study found that 5 days of insulin therapy which normalized blood glucose in newly diagnosed T2D increased TT by 3.28 nmol/L [116], establishing a bidirectional relationship. Similarly, a 2021 meta-analysis showed that diabetics compared to controls had lower semen volume, sperm total count, sperm concentration, and progressive motility [117], although subgroup analyses revealed that T2D was associated only with semen volume and progressive motility. Importantly, this meta-analysis showed that diabetes resulted in worse semen parameters than did obesity, indicating an additive effect of diabetes. An intervention study found that metformin improved semen parameters in men with metabolic syndrome [118], pointing to a link between insulin resistance and poor semen parameters. Testosterone deficiency may lead to insulin resistance via numerous mechanisms [119], and the resultant increase in oxidative stress may impair semen health [120]. High triglycerides and low HDL cholesterol, other signs of poor metabolic health, are associated with low TT independent of BMI [121, 122], although correlations with semen parameters are inconsistent [123, 124]. Hypertension, another component of metabolic syndrome, has been associated with poor semen parameters and lower TT [125, 126]. Animal models demonstrate that hypertension induces adverse changes in

testicular morphology and microcirculation, resulting in reduced semen quality [127]. Lastly, non-alcoholic fatty liver disease has been associated with low testosterone levels (OR = 4.52) and poor semen parameters, which appears to be independent of BMI and insulin resistance [128, 129], indicating an additive effect.

5. Dietary trends

The major shift in diet over the 20th century is an important environmental factor underpinning the rise in chronic diseases, particularly metabolic. At the same time, the links to MRH, discussed below (section 6), suggest that it is an important factor in the decline in MRH.

5.1. Industrialization and nutrition transition

Typically, when a country transfers from an agrarian to an industrial economy, this coincides with a nutrition transition in which diets shift from traditional agricultural to semi-refined and, finally, to modern processed foods. Although other changes accompany the nutrition transition, the increasing refinement of the diet is arguably the dominant factor. In the early stages of industrialization, refined ingredients, such as sugar, become readily available due to more efficient production methods, increased trade, and reduced costs [130]. In Britain, the first industrialized country, sugar availability can be seen increasing from 1700, and much more rapidly post-1840, mirroring the timeline of industrialization (Fig. 3) [58]. In the US, another country that industrialized early on, records starting in 1821 show similar increases (Fig. 3) [131]. Refined ingredients such as sugar increase palatability and energy intake [132, 133], leading to the first increases in obesity compared to pre-industrial levels [84]. As industrialization progresses, modern food processing techniques are utilized to create hyper-palatable, calorie-dense foods, often termed ultra-processed foods (UPFs) (including beverages) [134]. This began in Europe in the mid-19th century where industrial processes were used to create and mass-produce the first modern UPFs, such as chocolate bars and confectionery products [135]. From the 1950s onwards, consumption of UPFs grew more rapidly and later spread to developing countries (*circa* 1980), in part due to transnational food corporations [136, 137]. A large body of evidence indicates that such foods drive excess energy intake by overwhelming physiological mechanisms of satiety and appetite regulation, leading to a much more pronounced rise in obesity [138].

5.2. Trends in processed foods

The primary caloric ingredients in modern UPFs are typically added sweeteners (e.g., sugar and high-fructose corn syrup) and vegetable oils [139]. Global sugar availability data starting in 1860 and vegetable oil data starting in 1961 show large temporal increases (Supplementary Fig. 2, Fig. 4). More specific data from Canada, measuring household expenditure from 1938 to 2001, show that UPFs rose from 24.4 to 54.9% of total household food energy [11]. Using similar methods, a survey in Brazil found that from 1987 to 2003 UPFs rose from 18.7 to 26.1% of total household food energy [11]. These data highlight a difference between early (Canada) and late (Brazil) industrialized countries, with the former having UPFs as a major energy source for a longer time and with higher intakes. Supporting this, recent worldwide data (1998–2019) reveal that highly-industrialized countries have higher per capita UPF sales than less industrialized, developing countries [11, 134]. However, developing countries show larger increases in UPF sales [11, 134], illustrating a faster nutrition transition driven by the rapid industrialization of their economies [9] and food supply [134]. This mirrors the trends in obesity, diabetes, metabolic syndrome, and MRH, pointing to the rise in UPFs as a common etiological factor for these pathologies.

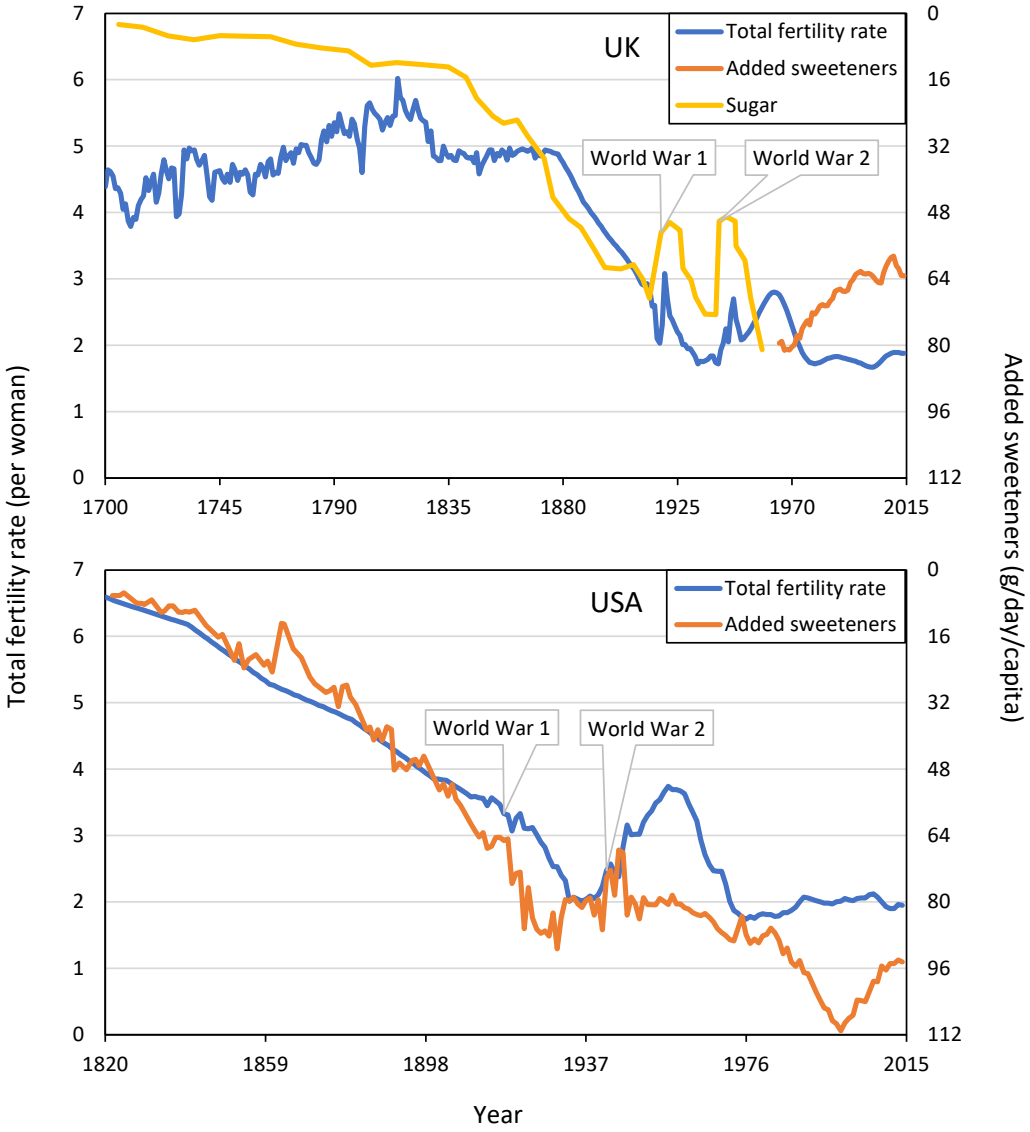

Fig. 3 UK (1700-2014) and US (1821-2014) sweetener availability, per capita vs total fertility rate. Added sweeteners include sugar, high-fructose corn syrup, and others. Food availability data loss-adjusted using mean 1970-2019 US Department of Agriculture sweetener loss rate (41%) [140]. Data from US Census Bureau, as sourced by Stephan Guyenet and Jeremy Landen (US, 1821-1908, added sweeteners) [131, 141], US Department of Agriculture (US, 1909-2014, added sweeteners) [140], Yudkin 1972 (UK, sugar) [142], United Nations (UK, added sweeteners, 5-year averages used) [143, 144], Gapminder version 6 (UK, 1700-1800, fertility rate) [80], and Gapminder version 12 (US and UK, 1800-2014, fertility rate) [81]

5.3. Global dietary trends

Global food availability data (1961-2019) reveal that the large temporal increase in vegetable oils is accompanied by a small decrease in animal fats, including more traditional fat sources such as butter, cream, and lard (Fig. 4). Moreover, the rise in sweeteners and grains, likely predominantly refined [145], is offset by a decrease in minimally processed carbohydrates, namely, starchy roots. Some positive trends do exist, such as the rise in fruit and vegetable intake, although the increase in fruit is partly driven by an increase in refined foods, such as fruit juice [146]. Meat shows a substantial increase, driven by pork and poultry consumption [143] and, along with small increases in eggs and fish, took protein from deficiency to sufficiency (170 vs 230 kcal/day) [147]. Geographical trends show that the nutrition transition is stratified by the rate and level of industrialization. Countries with high vs low industrialization show higher sweeteners, vegetable oils, meat, milk, eggs, alcoholic beverages, protein, fat and energy; lower starchy roots; and decreasing animal fats (Supplementary Fig. 3) [9, 58]. The global nutrition transition caused an increase in per capita energy (529 kcal/day), driven by an increase in carbohydrate (214 kcal) and fat (252 kcal) (Fig. 4). The initial increase in fat was likely driven by all fat types (saturated, monounsaturated, and polyunsaturated fatty acids, i.e., SFA, MUFA, and PUFA); however, recent global dietary survey data (1990-2010) indicate that SFA and trans-fatty acid (TFA) intake have stabilized, while n-6 PUFAs are still increasing [148]. The increase in total energy was partly beneficial as it brought some regions into nutritional sufficiency; however, the rise in processed food accounts for the majority of this increase in industrialized regions, and increasingly so in developing regions [11, 134]. This is arguably the leading cause of the global obesity and diabetes pandemics [18, 149, 150].

5.4. US dietary trends

The US represents an ideal case study for a more detailed examination of the effects of progressive industrialization for the following reasons: (1) it has a large population (331 million) [151], (2) it has long-term food availability data and dietary surveys, and (3) it pioneered many aspects of the industrialization of the food supply, including high-fructose corn syrup and soybean oil, and the growth of transnational food corporations (e.g., Coca-Cola, Kellogg's, and McDonald's) [130]. Food availability data (1909-2019) show a similar pattern to global trends, with increases in sweeteners, vegetable oils ('other fats and oils'), margarine, shortening, cocoa, frozen dairy products (e.g., ice cream), and soft drinks, all these being UPF ingredients or items (Supplementary Fig. 4). Similarly, unprocessed carbohydrates, such as potatoes, and traditional high-fat foods (e.g., butter, cream, lard, tallow, and whole milk) show temporal decreases. Interestingly, cheese shows a very large increase, ~2/3 of which is from UPFs and food consumed outside the home (e.g., fast food joints and restaurants) [152]. Industrially produced TFAs increased in usage from the 1930s to 1980s, reaching 6.8 g/day/capita in 1989 [153, 154], but have since been banned [155]. The NHANES dietary surveys which began in 1971 shed further light on the modern processed diet (*circa* 1980) [156], revealing that UPFs constitute 58% of total energy intake [157] and refined grains 86% of grain intake [158]. Mirroring global trends, this increasing refinement led to an increase in per capita energy (424 kcal/day), though in the US it was predominantly driven by an increase in PUFAs and MUFAs (Fig. 5). The increase in PUFAs was driven by linoleic acid, mainly derived from soybean oil, which increased from 2.2 to 7.2% of total energy availability (1909-1999) [159]. The increases in energy and PUFAs are supported by the NHANES data, although total fat (and thus MUFA) did not appear to increase post-1971 [160, 161]. This discrepancy is likely due to selective underreporting driven by social desirability bias [162].

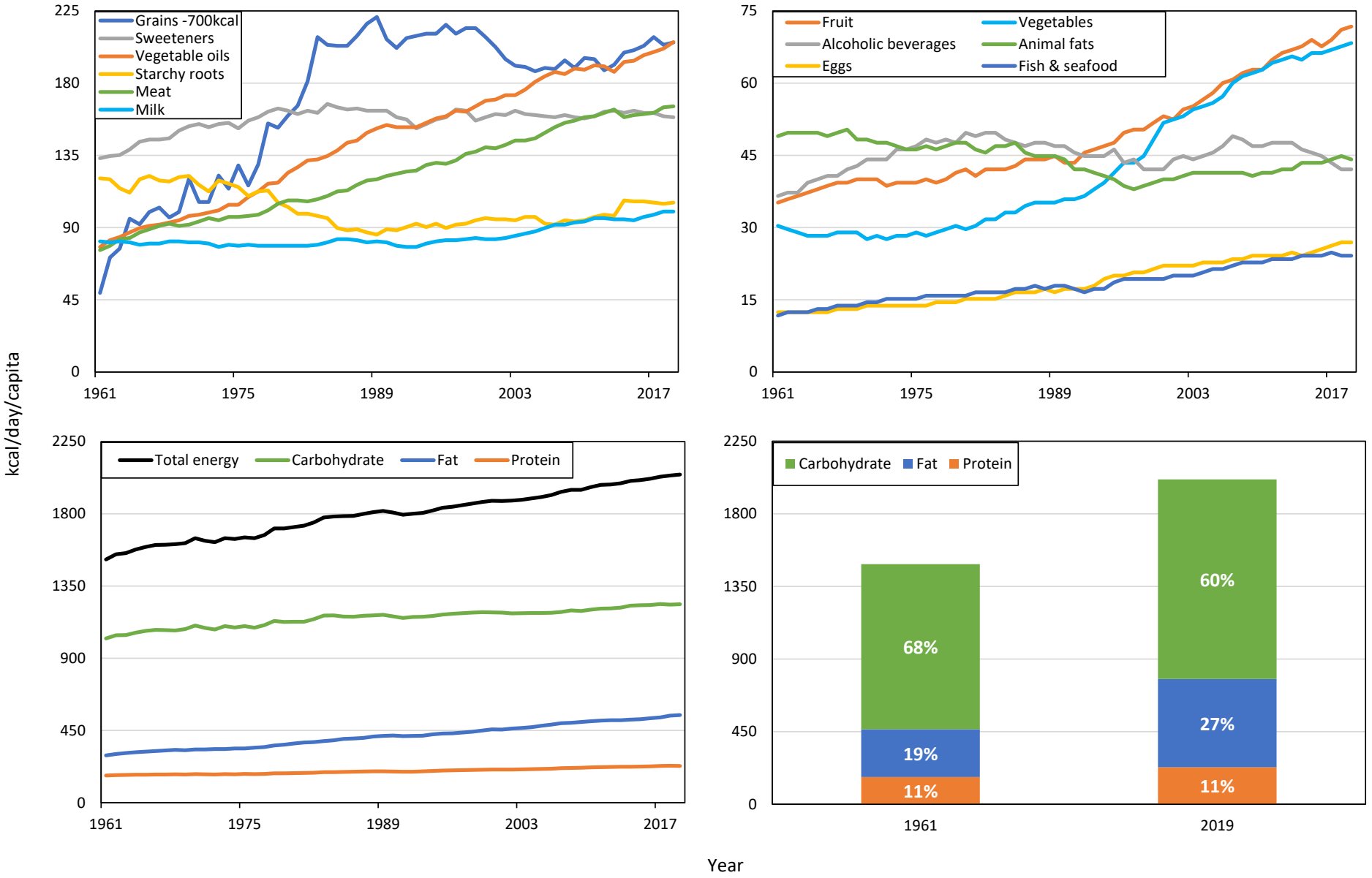

Fig. 4 Global food availability, per capita (1961-2019). Loss-adjusted using 2010 US Department of Agriculture total loss-rate (31%) [163]. Ethanol accounts for 2% of total energy over entire time period. Milk excludes butter. Data from United Nations [143, 144]

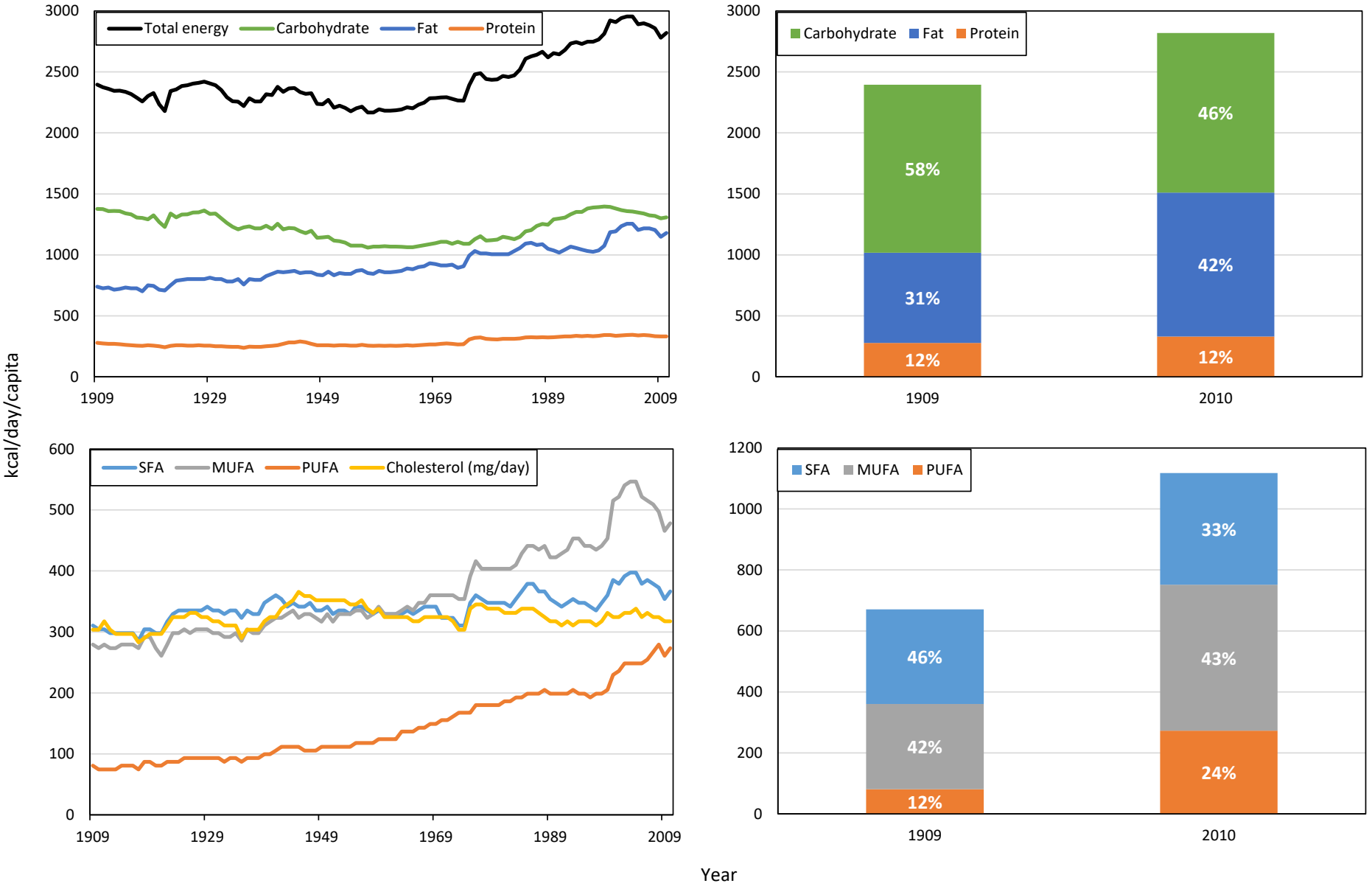

Fig. 5 US food availability, per capita (1909-2010). Loss-adjusted using 2010 US Department of Agriculture total loss rate (31%) [163]. Data from US Department of Agriculture [140]. Abbreviations: SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid

5.5. Farming and food production trends

Since the industrial revolution, there have been numerous changes to food production methods which, while increasing food security and supporting population growth [164], may have adversely affected health. These include the use of agrochemicals, high-yield crop varieties, and intensive livestock production systems [164–167]. Analyses of organic vs conventional foods provide a reasonable comparison of pre- vs post-industrial/modern foods. The largest and most rigorous meta-analysis on organic vs conventional crops identified 17% higher antioxidant activity, 5-69% higher phytonutrient content (depending on the compound), and 48% lower cadmium [168]. Meta-analyses of organic vs conventional meat and dairy have found ~50% higher n-3 PUFA in both [169, 170], which would result in ~5-12% higher total intakes in European populations [171], although organic dairy has 74% lower iodine [170]. Several studies on food composition data from industrialized countries have shown decreases in the mineral density of crops over the 20th century. Consistent decreases have been observed in iron and copper, along with various other decreases, ranging from ~10-50% [172–177]. This is likely caused by a 'dilution effect' of increasing crop yields [174]. For example, modern high-yield vs pre-1900 wheat has ~20-30% lower iron, zinc, selenium, and magnesium [178, 179]. Furthermore, the post-industrial trend towards increased food shipping distances and processing may have further reduced micro- and phytonutrient content [180–182]. However, as total food intake has increased over time, this may have offset any absolute decrease in nutrient intake. US (1909-2010) and global (1961-2011) nutrient availability data show temporal increases in micronutrients as well as in phytonutrient-rich fruits and vegetables (Fig. 4) [140, 183], although these data do not fully account for temporal trends in the nutrient density of foods. Taking this into account, a significant decline in micronutrient intake is possible though uncertain, a significant reduction in phytonutrient intake being more likely.

6. Diet and reproductive health

The literature indicates that diet and MRH are strongly linked. Thus, the dietary shift of the 20th century may have impaired MRH by direct effects, indirect effects via metabolic health, or, more probably, a combination of both.

6.1. Ultra-processed foods

Meta-analyses of observational studies show that higher UPF consumption is associated with an increased risk of obesity (OR = 1.55) [184], T2D (relative risk = 1.74) [185], and metabolic syndrome (OR = 1.79) [186]. Moreover, an analysis of 19 European countries found that a 1% increase in household UPF availability was associated with 0.25% increase in obesity prevalence [187]. A randomized controlled trial (RCT) (*n* = 20) using a 2-week *ad libitum* UPF vs unprocessed diet reported that 508 kcal/day higher energy intake, 1.8 kg difference in body weight, and biomarkers indicated increased insulin resistance, inflammation, and reduced satiety [188]. Several observational studies have noted that dietary patterns high vs low in UPFs are associated with worse semen parameters and reproductive hormones [189–194]. The largest of these (*n* = 7282) revealed that high sweetened snack and beverage consumption was associated with -5 million/ml median sperm concentration [190]. Another large study (*n* = 2935) found that high adherence to a western (high UPF) vs 'prudent' (low UPF) diet was associated with -68 million median total sperm count [192]. In addition, numerous observational studies have investigated the effect of sugar-sweetened beverages on male reproductive parameters, generally noting adverse effects [195–198]. For example, the largest study (*n* = 2935, same sample as [192]) observed that high sugar-sweetened

beverage consumption was associated with -13.2 million/ml median sperm concentration [195]. Another study reported that high vs low added sugar consumption from foods was associated with -6 million/ml sperm concentration [199]. Although these studies lack consistency as to which reproductive parameter is affected by UPFs, probably due to diverse methodologies, overall, they strongly indicate that UPFs adversely affect MRH. Moreover, since many of these studies are adjusted for BMI and energy intake and exclude men with comorbidities (metabolic and others), they likely underestimate the true adverse effects of UPFs on MRH. For instance, one study found that a high UPF diet was associated with lower TT and impaired kidney function, highlighting the link between UPFs, poor reproductive health, and comorbidities [200].

6.2. Polyunsaturated fats

US population-based data show that secular increases in linoleic acid availability are reflected in adipose tissue concentrations, which increased from 9.1 to 21.5% (1959-2008) [201]. Interestingly, a 2020 review reported that reproductively impaired men vs controls had higher n-6 and lower n-3 PUFA semen levels [202]. Studies in rodents and humans demonstrate that dietary PUFAs modify semen and testicular lipid composition [203–206]. RCTs using n-3 PUFA supplements have found clinically significant improvements in semen parameters [207, 208], with such changes correlating to n-3 PUFA levels in semen and red blood cells [205], this illustrating the link between PUFAs, cellular fatty acid composition, and MRH. In addition, RCTs have found that n-3 PUFA supplements decrease markers of inflammation and oxidative stress [209, 210], both of which are implicated in the pathogenesis of male infertility [211], suggesting possible mechanisms. In contrast, the effects of n-3 PUFAs on testosterone are inconsistent, with some RCTs showing a beneficial effect [212] and others no effect [205, 208]. Studies in rodents have reported that high n-6 PUFA diets increase testicular oxidative stress, lower testosterone, and impair semen parameters [203, 204, 213]. Moreover, consumption of heated and oxidized vegetable oils in rodents produces multiple male reproductive abnormalities [214, 215], high-PUFA oils being more prone to oxidation [216]. Though direct human intervention studies on n-6 PUFAs and MRH are lacking, some studies indicate that high vs low PUFA: SFA ratio diets may decrease TT [6, 217]. Furthermore, high vs low n-6 PUFA diets increase markers of oxidative stress [218, 219], it being well known that oxidative stress may impair male fertility [220]. Thus, animal studies and indirect evidence indicate that n-6 PUFAs impair MRH; however, this remains to be proven in direct intervention studies.

6.3. Saturated and monounsaturated fats

Some observational studies have associated high vs low SFA intake with worse semen parameters [221–223], others, however, showing reverse results [224]. A larger study (*n* = 1907) found that consuming high SFA foods (e.g., red meat and whole milk) decreased the risk of poor sperm morphology (OR = 0.67) [225]. Observational research concerning SFAs may be subject to a healthy user bias [226] as SFAs are generally viewed as unhealthy [227]. This bias is difficult to overcome without intervention studies and may explain the former results. As regards MUFAs, observational research has found little association with semen parameters [222, 224]; however, one RCT noted that the Mediterranean diet, which is generally high in MUFAs, improved semen parameters [228]. Another RCT observed that a Mediterranean vs low-fat diet (39 vs 30% fat) resulted in greater improvements in sperm concentration (1.93 million/ml) and total count (8.02 million) [8]. As concerns testosterone, a meta-analysis of intervention studies reported that low- vs high-fat diets (20 vs 40% fat), of which the majority was MUFAs and SFAs, decreased TT and free testosterone [6]. The beneficial effects of SFAs and MUFA on testosterone are also supported by the aforementioned animal research (section 6.2) [203, 204]. Thus, the secular increase in SFAs and MUFAs is unlikely to

have adversely affected MRH, although intervention studies on SFAs and semen parameters are lacking.

6.4. TFAs

TFAs account for ~1.4% of global total energy intake and, although industrially produced TFAs have been phased out in many countries, their usage has increased in some developing regions [148]. High vs low TFA consumption has been associated with -55 million total sperm count [224], -31 million/ml sperm concentration [229], and -3.4 nmol/L TT [230]. TFA intake is correlated with sperm and seminal plasma TFA levels (r = 0.26, r = 0.44) [229], and sperm TFA levels are inversely correlated with sperm concentrations (r = -0.44) [231]. Rodents fed hydrogenated vegetable oil vs butter, sunflower, or rapeseed oil show higher TFA levels in adipose tissue, reduced TT, and higher abnormal sperm morphology, indicating causation [232]. Thus, as evidenced by animal and observational studies, the rise in TFAs from partially hydrogenated oils during the 20th century is likely to have impaired MRH.

6.5. Micronutrients

Since it is possible that micronutrient intakes may have decreased in the post-industrial period, it is worth exploring the implications of this. Intervention studies using dietary supplements best elucidate the effects of micronutrients on MRH. RCTs on selenium have generally found improvements in sperm motility (4–7.6%) [233–235], and the largest RCT observed additional improvements in concentration (5.2 million/ml) and normal morphology (2%) [234]. Zinc has more varied results, with some RCTs showing improvements in semen parameters [236], although others have not, besides a reduction in abnormal sperm chromatin (5.3%) [237, 238]. A large RCT (n = 2370) using zinc and vitamin B9 failed to show an improvement in semen parameters and live birth rates [239], even though it has long been proven that zinc deficiency decreases TT [240]. Individual RCTs have found that vitamins C and E decrease sperm DNA fragmentation [241], vitamin E improves zona binding ratio [242], and vitamin C improves normal morphology [243]. As regards B vitamins, a meta-analysis observed that B9 increased sperm concentration [244], a trial found that B12 improved sperm concentration in 57% of oligozoospermic men [245], and an RCT noted that inositol improved several semen parameters and reproductive hormones [246]. Nutrients may offer greater benefits when combined; for instance, an RCT reported that improvements in sperm motility were greater with a multivitamin vs coenzyme Q_{10} (9.8 vs 6.3%) [247]. In addition, a small trial using azoospermic men showed that a combination of a multivitamin, coenzyme Q_{10}, and lemons increased sperm concentration by 9.7 million/ml, resulting in two pregnancies among the nine men who were followed up [248]. Regarding conception, a Cochrane review of RCTs found that antioxidant supplements increased pregnancy (OR = 1.89) and live birth rates (OR = 1.43) [249]. These outcomes were partly dependant on nutrients in which temporal declines are unlikely, such as coenzyme Q_{10} and carnitine, but also encompassed micronutrients including selenium, zinc, and vitamins E and C.

Observational research has revealed that seminal B6 is 77% lower in asthenozoospermic men vs controls [250], iodine deficiency being associated with 58% and 52% lower sperm concentration and total count [251]. The other micronutrients are either not well studied individually or lack consistent effects in intervention or observational studies [252–255]. Other research has noted that infertile vs fertile men have 61% and 40% lower blood vitamin C and E, 13% lower hair zinc, and 12% higher hair selenium (suggesting pre-deficiency) [256]. This illustrates the fact that temporal decreases in food nutrient density of the magnitude previously discussed (section 5.5) may have significantly impaired MRH. For example, 500 kcal of 1840s organic wholewheat vs modern conventional white flour provides 68 vs 10% of the UK's recommended zinc intake (figures calculated) [147, 179, 257].

6.6. Phytonutrients

Similarly to micronutrients, intervention studies using supplements or specific foods best illustrate the effects of phytonutrients. RCTs have found that lycopene supplements increase sperm normal morphology (6%) [258], and curcumin supplements increase sperm total count (10.8 million/ml), concentration (3.2 million/ml) and motility (5.3%) and decrease markers of oxidative stress and inflammation, indicating possible mechanisms [259]. Moreover, a pilot study using a resveratrol-based multivitamin reported improvements in sperm total count, concentration, and motility [260]. Three RCTs on nut consumption (mainly walnuts) have observed consistent increases in sperm motility (3.4-9.1%) and, to a lesser extent, normal morphology (0.7-1.1%) [261–263]. Nuts contain a variety of nutrients, being in particular a rich source of phytonutrients, with especially walnuts having a very high phenolic content [264]. Another RCT found that 5ml/day of *nigella sativa* seed oil, a phytonutrient rich food, increased sperm concentration (16.7 million/ml), normal morphology (9.6%), and motility (6.3%) [265]. The literature on testosterone is more limited; nevertheless, a meta-analysis of four RCTs reported that fenugreek extract supplements increased TT, indicating that glycoside phytochemicals may modulate testosterone levels [266]. These studies show links between certain phytonutrients and MRH, while observational research points to dietary phytonutrient intake possibly playing a significant role in male infertility. It is important to note, for instance, that higher intakes of carotenoids (β-carotene, lutein, and lycopene) are associated with better semen parameters [267–269] and infertile vs fertile men have lower plasma carotenoid levels [270].

6.7. EDCs and heavy metals

Exposure to EDCs and heavy metals, many of which are diet-derived, has substantially increased during the post-industrial era [3, 271]. EDCs in plastic packaging leach into liquids and perhaps also dry foods [272, 273], while, in addition, other modern food packaging materials, such as recycled paperboard, leach EDCs into food [274]. Phthalates, found in most plastics, are higher in semen of infertile vs fertile men and decrease sperm motility at comparable concentrations in vitro [275]. Regarding pesticides, a study reported that high intake of fruit and vegetables low in pesticides was associated with 146.8 million and 51.9 million/ml higher sperm total count and concentration, whereas that of fruit and vegetables high in pesticides was unrelated to semen parameters [276]. Another study found that urinary pesticide metabolites were inversely correlated with sperm total count, concentration, and motility [277], and in vitro, animal, and human case studies have demonstrated that high-dose occupational pesticide exposure may result in male infertility [278, 279]. In contrast, a causal relationship between low-dose pesticide exposure and impaired MRH is currently unclear. Turning to heavy metals, fish and seafood are the primary sources of exposure to mercury in the general population, besides dental fillings [280]. Observational research shows that higher mercury exposure is associated with worse semen parameters [281], while it is well established that mercury causes male reproductive impairment in animal models [282]. However, observational studies are conflicting as to whether the benefits of fish consumption (n-3 PUFAs) outweigh the adverse effects of mercury exposure [283–285]. Cadmium is another heavy metal that humans are primarily exposed to via diet (besides via smoking) [286]. A meta-analysis reported that infertile vs fertile men had moderately higher semen cadmium [287], while animal studies show that low-dose cadmium exposure causes decreased sperm motility [288]. Additionally, EDCs and heavy metals may impair metabolic health [289, 290], suggesting that they may directly and indirectly decrease MRH.

6.8. Intergenerational effects of diet

Pioneering studies in the 1940s showed that cats placed on sub-optimal diets exhibited progressive degeneration when bred for several generations. This degeneration included impairments in metabolic and reproductive health, which, by the third generation, rendered all cats infertile [291]. Anthropological studies from the 1930s demonstrated in a wide variety of human populations similar degenerative changes when non-industrialized populations were exposed to industrial diets, although reproductive changes were not as robustly examined [292]. Later studies on the Dutch famine and Överkalix cohorts found that the grandmother's exposure to famine during gestation was associated with increased neonatal adiposity (+1.4 kg/m^3) and poor health in later life in grandchildren (OR = 1.8) [293], while the grandfather's exposure to high food availability in childhood increased the risk of diabetes-related mortality in grandchildren (OR = 4.1) [294], the results illustrating the intergenerational effects of diet. Rodent studies have reported that maternal and paternal obesity and diabetes result in multiple reproductive impairments in male offspring [295–298] and that grandpaternal obesity and diabetes also impairs MRH in offspring [296, 297]. However, the effects grandmaternal obesity and diabetes on MRH in offspring are less studied.

In humans, observational studies have associated maternal overweight/obesity with a higher risk of male infertility (OR = 1.4) and earlier pubertal timing (~8 months) [299, 300]. Maternal and paternal obesity and diabetes and grandparental obesity also substantially increase the risk of such diseases in offspring [301–304]. Rodent studies have shown a high UPF maternal diet results in low testosterone and sperm abnormalities in male offspring [305, 306], and a human study associated consumption of fast food with adverse epigenetic changes in sperm [307]. TFAs in rodents cause low testosterone and poor sperm morphology in male offspring, the latter becoming magnified across subsequent generations [232]. Additionally, due to the advent of infant formula in 1867 and its rise in popularity, breastfeeding subsequently decreased to a nadir in the early 1970s, in the US [308]. Since then, breastfeeding rates have partially recovered in high income countries, although they are still substantially lower than those in middle and low income countries [308, 309]. Two observational studies have associated shorter breastfeeding duration with small adverse changes in adult male reproductive hormones [310, 311], while breastfeeding decreases the offspring's risk of overweight/obesity (OR = 0.74) and T2D (OR = 0.65) [312]. Relatedly, EDC exposure via breast milk is associated with worse semen parameters and a higher risk of cryptorchidism [313, 314], and high maternal beef consumption is associated with 13.8 million/ml lower sperm concentration in sons, possibly due to prenatal exogenous steroid exposure [315], indicating further intergenerational effects.

7. Common mechanisms

The concurrent temporal trends along with observational and experimental data suggest that there are common underlying mechanisms driving the associations between metabolic and reproductive health, which are partly driven by dietary factors.

7.1. Insulin resistance

Controlled feeding studies illustrate that short-term overfeeding induces insulin resistance in the absence of exercise [316, 317]. UFPs are thought to stimulate higher energy intakes due to their hedonic properties and lower satiety per kcal, resulting from their higher energy density, refined

ingredients, and flavor enhancers and combinations, this observation often termed the food reward hypothesis [133, 318–320]. For example, an RCT found that high-sugar beverage consumption resulted in a decreased striatal response to such beverages [321], while another study reported that the energy density of foods was inversely correlated with satiety ratings [133]. Obesity appears to increase insulin resistance via elevated plasma free-fatty acids from adipose tissue, which cause increased lipid oxidation at the expense of glucose uptake in skeletal muscle [90]. The resultant hyperglycemia incurs hyperinsulinemia, which increases insulin resistance, also resulting in increased glycation end products which damage pancreatic β-cells, leading to insulin deficiency [90]. Hyperglycemia caused by insulin resistance is well known to increase oxidative stress [322]. Markers of oxidative stress are higher in semen of diabetics [323], including advanced glycation end products, which correlate with oxidative stress and are likely partly responsible for the impaired fertility [324]. Furthermore, men with T2D have substantially higher semen leukocytes, with a higher percentage of T-suppressor and lower T-helper lymphocytes [325], indicating an immuno-inflammatory component of the pathogenesis; polymorphonuclear leukocytes are also capable of producing large amounts of reactive oxygen species [326]. Insulin resistance may impair the hypothalamic-pituitary-gonadal axis at the level of the testes, specifically in regard to the Leydig cells. One study observed that insulin sensitivity was associated with the testosterone response to exogenous human chorionic gonadotropin, though not with the luteinizing hormone response to exogenous gonadotropin-releasing hormone [327]. Moreover, insulin resistance may disrupt the hypothalamic-pituitary-gonadal axis in other areas, namely, the hypothalamus or pituitary gland.

7.2. Oxidative stress

Oxidative stress is a key competent of the pathogenesis of male infertility, as sperm cell membranes contain high amounts of PUFAs and have low intracellular antioxidants rendering them particularly susceptible to oxidative damage [328]. Rodent studies indicate that high n-6 PUFA diets induce complex alterations in testicular lipid composition, including the double-bond index. This results in increased markers of oxidative stress, decreased 3β- and 17β-hydroxysteroid dehydrogenase activity, the key steroidogenic enzymes responsible for testosterone synthesis, and decreased testicular free cholesterol and cholesterol ester, which strongly correlate with reduced testosterone production [203, 204]. Moreover, rodents fed diets with either high or very low n-6:n-3 PUFA ratios, have impaired sperm quality and adverse testicular histological changes [213]. PUFAs are capable of modulating sperm fatty acid composition; meanwhile, higher n-6:n-3 PUFA ratios may increase the susceptibility of sperm cell membranes to oxidative damage while also exerting other adverse effects on spermatogenesis [205, 206, 329, 330], possibly mediated via increased proinflammatory signaling, leading to free radical production [331, 332].

Several micronutrients have well-established roles in the human redox system. Two of the three classes of seminal antioxidant enzymes are dependant on minerals [328]. Intracellular superoxide dismutase (SOD1) and extracellular superoxide dismutase (SOD3) are formed of copper and zinc ions; intracellular superoxide dismutase (SOD2) is formed of manganese ions: it has only negligible activity [328, 333]. Meanwhile, glutathione peroxidase 1-4 and 6 contain selenium, with 4 appearing to be the most important [334]. Superoxide dismutase neutralizes superoxide anion, both intra- and extra-cellularly, protecting sperm from lipid peroxidation and motility loss [335]. Glutathione peroxidase neutralizes hydrogen peroxide and organic peroxides, protecting sperm from lipid peroxidation, while it aids in chromatin compaction and helps form the mitochondrial sheath of sperm [334, 336]. In terms of non-enzymatic antioxidants, vitamin E is an important chain-breaking antioxidant capable of neutralizing superoxide anion, hydrogen peroxide, and hydroxyl radicals, thereby protecting sperm cell membranes from lipid peroxidation [328, 335]. Vitamin C, another

chain-breaking antioxidant, protects against peroxyl radicals and recycles vitamin E [335]. Phytonutrients are another important class of molecules as regards oxidative stress. Carotenoids can directly neutralize singlet oxygen and peroxyl radicals and stimulate endogenous enzymatic antioxidants via transcription factors [337], which may protect sperm cell membranes and lipoproteins from peroxidation, among other effects [338]. Interestingly, a meal of ice cream vs avocado increased post-prandial plasma oxidative activity [339], indicating that phytonutrient-poor UPFs may impair redox balance. In addition, an RCT in children noted that an organic diet decreased markers of oxidative stress and inflammation [340], which may be modulated via the higher phytonutrient content of organic foods [168, 341]; however, this study also reduced energy intake, which is a potential confounding variable [340].

7.3. Inflammation

Inflammation and oxidative stress are closely linked, with both capable of inducing the other [342]. For instance, phagocytes induce localized free radical production in 'oxidative bursts' during microbe destruction [332], whereas reactive oxygen species can activate nuclear factor kappa B [343]. Both inflammation and oxidative stress are necessary for normal physiologic function; however, chronic inflammation, often accompanied by increased oxidative stress, is implicated in the pathology of several chronic diseases [342], including male infertility [211]. Free radicals produced during inflammatory processes may be emitted extracellularly by leukocytes [332], with the potential to cause oxidative damage to sperm and other reproductive cells. Moreover, proinflammatory cytokines may downregulate catalase and upregulate xanthine oxidase, shifting redox balance to an oxidative state [344]. The primary cytokines that modulate inflammation in the male reproductive system are tumor necrosis factors and interleukins, which may have direct adverse effects on MRH [345]. In Leydig cells, tumor necrosis factor-α activates nuclear factor kappa B, which inhibits orphan nuclear receptor transactivation, leading to repressed steroidogenic enzyme gene expression [346]. Interleukin 1-α can disrupt Sertoli cell actin cytoskeletons and impair the blood-testis barrier [347] which, among other regulatory functions [345], may explain why interleukin-1 receptor antagonist knockout mice have poor sperm morphology and reduced fertilization ability [348].

Adipose tissue secretes proinflammatory adipocytokines, including tumor necrosis factor-α and interleukin-6, with secretion being higher in obesity [349]. Interleukin-6 can disrupt the blood-testis barrier [350], while it has been observed that obese mice have higher interleukin-6 in serum and testis, which disrupts spermatogenesis via inhibition of Zfp637 expression [351]. Tumor necrosis factor-α may impair hypothalamic kisspeptin receptor expression and ciliogenesis, thereby reducing gonadotropin-releasing hormone secretion [352]. Supplementation of micronutrients decreases markers of systemic inflammation, these including zinc [353], selenium [354], vitamin E [355], and vitamin C [356]. Interestingly, the latter micronutrients are all important nutrients for MRH (section 6.5), suggesting an inflammation-based mechanism underlying their beneficial effects. Zinc plays a key role in inflammatory processes, including inhibition of nuclear factor kappa B activation via protein A20 expression, interleukin-6 activated signal transducer and activator of transcription-3, and caspase apoptosis [357]. Vitamin C decreases interleukin-6 and tumor necrosis factor-α, and increases interleukin-4 and transforming growth factor-β gene expression in sperm, shifting gene expression to an anti-inflammatory state [358]. Phytonutrient supplements, phytonutrient-rich foods, and fruit and vegetable consumption appear to decrease markers of inflammation [359, 360], possibly via synergistic neutralizing of inflammation-derived free radicals, subsequently decreasing nuclear factor kappa B and ERK activation [361]. Industrially produced TFAs consistently elevate markers of inflammation [362], likely by activating apoptosis signal-regulating kinase-1, leading to proinflammatory signaling and apoptosis [363]. On the other hand, increased n-6 PUFA intake is not

clearly associated with elevated markers of systemic inflammation [364], suggesting that any adverse effects on MRH are meditated via localized signaling (section 7.2).

7.4. Epigenetic inheritance

Intergenerational environmental effects may be divided into two categories, namely, (1) maternal and (2) paternal and grandparental, the former incorporating direct in utero and post-natal environmental exposures. Epigenetic inheritance is arguably the dominant mode of intergenerational environmental transmission, although other mechanisms do exist, such as microbiome transmission [365]. In rodents, maternal obesity increases body fat and insulin resistance in offspring, even when the latter are fed a standard diet; this effect is magnified when they are fed an obesogenic diet, which effect is greater than that of offspring of lean mothers [366]. Maternal obesity results in hypermethylation of the proopiomelanocortin gene in both the enhancer and the promoter regions, with the latter change, near specificity protein 1 binding site on the gene, persisting into adulthood. This may decrease leptin-induced increases in proopiomelanocortin expression, resulting in impaired appetite regulation and hyperphagia [367]. Maternal obesity induces numerous other adverse epigenetic changes in rodent offspring, contributing to poor metabolic health, including hypermethylation of metalloproteinase-9 [368], histone modification of serum paraoxonase and arylesterase-1 [369], and modifications of the leptin gene [370]. These animal data are corroborated by human studies, which, however, are more limited in scope. For example, the methylation profile of adiponectin and leptin genes in placenta tissue has been associated with maternal glucose levels and insulin sensitivity [371, 372], and expression of 27 micro-RNAs in mid-pregnancy peripheral blood samples, including several associated with adipogenesis, is positively associated with pre-pregnancy BMI [373]. Interestingly, the duration of breastfeeding is inversely correlated with methylation of leptin gene in 17-month-old infants [374], which may partly explain breastfeeding's association with reduced obesity risk [312].

Although paternal and grandparental effects are typically weaker than maternal in utero and post-natal effects, they do appear to have an additive impact. For instance, in rodents, maternal and paternal obesity combined results in worse adiposity and insulin resistance in offspring than either alone [375]. Furthermore, over consecutive generations of paternal obesity, body weight and insulin resistance progressively increase, which corresponds to epigenetic modifications on leptin (mono-methyl H4K20) and adiponectin (acetyl H3K9) gene promoter regions, increasing and decreasing gene expression, respectively [375]. Paternal and grandpaternal transmission of adverse metabolic phenotypes may also be transmitted via small-RNAs in sperm, including diet-sensitive transfer RNA fragments [376]. Recent studies on paternal obesity and MRH in rodent offspring, although falling short of elucidating epigenetic inheritance mechanisms, do provide a basis for them. Paternal diabetes increases testicular gene expression of nuclear transition protein 2 and protamine 1, with the latter persisting in grandchildren [297], while paternal obesity alters the testicular metabolite profile, which correlates with sperm quality, and persists in grandchildren [377]. Moreover, epigenetic changes that impair metabolic health may lead to poor MRH via the mechanisms already discussed (sections 7.1, 7.2, 7.3). Underlining this point, maternal obesity rodent offspring concurrently suffer from increased adiposity, insulin resistance, sperm and testicular oxidative stress, low testosterone, and poor semen quality despite a standard diet [295, 366].

8. Discussion

The results of this review demonstrate that MRH has undergone a substantial decline over the 20th century, which has coincided with a large increase in obesity, diabetes, and metabolic syndrome in industrialized countries. Industrialization results in a nutrition transition from an agrarian unprocessed to a modern processed diet, including increases in sugar, vegetable oils, UPFs, TFAs, n-6 PUFAs, and total energy. These dietary changes have significantly impaired metabolic and reproductive health via increased inflammation, oxidative stress, and insulin resistance. Moreover, the adverse health effects of the dietary shift appear to amplify across subsequent generations via epigenetic inheritance, leading to a progressive decline in reproductive function. Previous reviews have found that prudent dietary patterns including greater intakes of fruit, vegetables, nuts, fish, poultry, and low-fat dairy are associated with better MRH [20, 21]. However, since these foods have increased in consumption over the 20th century (Supplementary Figs. 3 and 4), they are unlikely to be causal factors in the decline in MRH. The present review finds instead that UFPs, TFAs, n-6 PUFAs, and higher total energy are both associated with poor MRH and have increased in consumption over the 20th century, meaning that they are potential causal factors in the decline in MRH. Industrialization itself may only be a risk marker for impaired MRH, that is, an association; however, many environmental changes within the industrialization process are potential risk factors for poor MRH, that is, potential causes. These include decreased physical activity, increased psychological stress, exposure to toxins, and disrupted circadian rhythms [3, 10, 12, 13], all of which are strongly linked to impaired fertility [3, 378–380]. Thus, post-industrial environmental changes are highly likely to represent a matrix of interrelated causes of the secular decline in MRH.

An alternative explanation for the decline in sperm counts has been proposed which is known as the sperm count biovariability hypothesis [381]. In essence, this hypothesis states that sperm counts vary across populations and time periods within a non-pathological range, and that declines found in meta-analyses may be due to such variation [381]. However, this hypothesis does not fit the data covered in this review. Firstly, if the data points included in these meta-analyses were subject only to variation, or even increased variation over time, then no statistical decline would be found. The different samples taken over time would represent mere fluctuation and no downward trend would be present in regression analysis. Secondly, given a stable Gaussian distribution of data, a lower mean value would shift the whole set of values lower. Therefore, a mean sperm concentration of 46.8 vs 100.3 million/ml, corresponding to western countries in 2015 vs 1973 [25], indicates a substantially higher proportion of men below the normal range (<15 million/ml) [382]. Contemporary data from Finland and Demark show 9.1% and 15% of young men have sperm concentrations <15 million/ml [383]. However, fertility starts to decline below ~50 million/ml [384, 385], implying that the majority of western men have impaired fertility compared to their counterparts in 1973. Lastly, given the adverse trends in other semen parameters (i.e., total count, volume, motility, and morphology) and markers of reproductive health (i.e., testosterone, reproductive pathologies, twinning rates, and medically assisted reproduction; section 2), a holistic view of the current evidence strongly indicates a substantial decline in MRH.

The question of how much of the decline in MRH is due to dietary factors is difficult to answer. Two studies showed no decline in TT after BMI adjustment [35, 46], whereas five studies still showed a decline after BMI adjustment, although often attenuated [33, 37, 45, 47, 48] (Table 1). In western countries, male BMI increased by 3.1 kg/m^2 from 1975-2016 [83, 386], which, based on meta-analysis data [7], would be expected to decrease TT by ~2.87 nmol/L. Temporal semen studies are not typically adjusted for BMI; however, using recent RCT data [108], the post-1975 increase in BMI may be expected to decrease sperm concentration by ~13.2 million/ml and total count by ~59.4

million, although this estimate is based on weight loss in class 2 obesity. Regarding the effects of diet quality, pertinent studies on testosterone are sparse. However, an RCT using a Mediterranean diet, similar to a non-industrialized diet for that region, found that sperm concentration increased by 2.4 million/ml and total count by 9.1 million [8]. This intervention slightly reduced energy intake (-295 kcal/day) but observed no significant changes in blood glucose or lipids and used non-obese men, indicating that increased diet quality rather than reduced energy intake was predominantly responsible for the improvements. Thus, taking the most rigorous meta-analysis to date, which showed that sperm concentration decreased by 53.5 million/ml and total count by 197.6 million in western countries (1973-2015)[25], and adding the results of the two aforementioned RCTs together (energy intake [108] + diet quality effects [8]), dietary factors may account for up to ~30% of the decline in semen parameters (15.6 million/ml sperm concentration; 68.5 million total count). Furthermore, considering the effects of BMI adjustment on secular decline TT studies (Table 1), this appears a reasonable estimate for testosterone, although long-term and intergenerational dietary effects may be in addition to this estimate.

It is well established that industrialization causes a fertility transition in which fertility rates decrease from ~5 to 2 births per woman [59, 60]. As the world continues to industrialize, it is expected that all geographical regions will eventually reach <2 births per woman, which has been the average in Europe and North America since the 1980s (Fig. 2). While the previous literature on the fertility transition has focused on economic, demographic, and cultural explanations [59, 60], recently, biological explanations have started to be examined [3] exploring whether a decline in fecundity has contributed to the decline in fertility rates. Historical data from the UK and US show that the nutrition transition, as identified by the rise in sugar availability, coincided with the fertility transition in these countries (Fig. 3), although France is an outlier in this respect [81, 387]. It is tempting to speculate that the nutrition transition caused by the industrialization of the food supply adversely affected reproductive health and contributed to the decline in fertility rates. In support of this hypothesis, post-1961 fertility rates stratified by year and country, correlated against key aspects of nutrition transition (increasing BMI and total energy), display significant correlations, thus accounting for approximately half of the variance (Fig. 6). Although these analyses are marred by many confounding variables, such as the rise in contraception, they are suggestive of a causal link which, along with the other adverse effects of industrialization on reproductive health, may explain part of the fertility transition. This hypothesis needs to be explored via further research utilizing robust research approaches.

The current review has highlighted the adverse effects of industrialization on health. However, there have been numerous benefits to increasing industrialization and technological progress over the 20th century. These include the development of essential medicines, antibiotics, and vaccines, improved sanitation, emergency medicine, obstetrics, and food security [164, 388, 389], which have led to an increase in life expectancy from ~35 years (pre-industrial) to ~80 years (21st century) in high-income countries [390]. This has largely been due to reductions in childhood mortality (>5 years), which decreased from ~30% (pre-industrial) to <0.5% (21st century) in high-income countries [391, 392], and in deaths from communicable diseases, which, along with neonatal and 'other deaths', decreased from 78 to 33% of deaths in the US (1900-1998, top 10 causes of death) [393, 394]. Arguably, these gains have been predominantly due to scientific progress and public health measures rather than to improvements in environmental factors, besides basic nutritional sufficiency. In fact, the modal age of death in both pre-industrial Europe and 20th century hunter gatherers was ~72 years, indicating that this is *homo sapiens*' adaptive lifespan [395].

It is important to put the results of this review into a clinical perspective, since, although some effects may be statistically significant, due to their small effect sizes they are clinically insignificant. The average TT is ~13 nmol/L [396] and the normal range is 9.2-31.8 nmol/L [397]. However, reference ranges derived from men with normal semen parameters and reproductive function are slightly higher, namely, 10.4–30.1 nmol/L [398]. The average contemporary sperm concentration for western men is 46.8 million/ml, total count 153.3 million, normal morphology ~7%, and total motility ~75% [25, 383], while normal ranges are ≥15 million/ml, ≥39 million, ≥4%, and ≥40% respectively [382]. However, sperm concentrations up to ~50 million/ml and normal morphology up to ~50% increase the chance of pregnancy [384, 385]. Weight loss for both testosterone and semen parameters appears to have a substantial effect, increasing TT by ~2.87 nmol/L [7] and sperm concentration by ~13.2 million/ml [108]. This is pertinent given that the average male BMI in western countries is 27.8 kg/m^2 [83, 386]. N-3 PUFA supplements generally improve at least one semen parameter to a clinically significant degree in RCTs [207, 208]. The effects of individual micronutrients on semen parameters tend to be small and inconsistent (section 6.5), although when combined they appear to offer greater benefits [247, 248]. Moreover, their positive relationship to pregnancy and live birth rates [249] points to a clinically significant effect. Phytonutrient supplements typically have larger effects on semen parameters (section 6.6), and intake of nuts results in clinically significant increases in motility (3.4-9.1%) [261–263]. Thus, diets rich in micronutrients, phytonutrients, nuts, n-3 PUFAs, carnitine, and coenzyme Q_{10} may improve MRH. Additionally, combining multiple nutrients may have a synergistic benefit. Maintaining a healthy weight is also important, which may be achieved by increasing wholefoods and decreasing UPFs [188], which would increase micro- and phytonutrient intake as well [399, 400].

The evidence used in this review was selected first based on relevance and second on quality, with a preference for intervention over observational studies. Although there are numerous dietary intervention studies on male reproductive hormones, there is a distinct lack of such studies concerning semen parameters. Moreover, intervention studies on male reproductive hormones often focus on different macronutrient ratios (e.g., low-fat and low-carbohydrate) rather than on different diets (e.g., Mediterranean, vegetarian, and Palaeolithic). Thus, future research should examine the effects of different diets in addition to the macronutrient ratios that typically come with such diets. Moreover, different diets should be rigorously compared to determine which is superior, as most dietary changes will elicit positive effects when compared to the modern processed diet. Much of the research to date has focused on semen parameters as proxies for male fertility typically due to their ease of measurement and sensitivity to change. Where possible, studies should also examine the effects of nutrition on time to pregnancy and live birth rates, these being the end goal.

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Conflicts of interest

The author reports no declarations of competing interest.

Ethics approval

This research did not require ethical approval, as it used only previously published data.

Availability of data and material

This research used only publicly available data; the sources are cited within the article and any amendments are noted where relevant. The curated dataset for Fig. 6 may be requested from the author.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Code availability

Not applicable.

Author contributions

Not applicable.

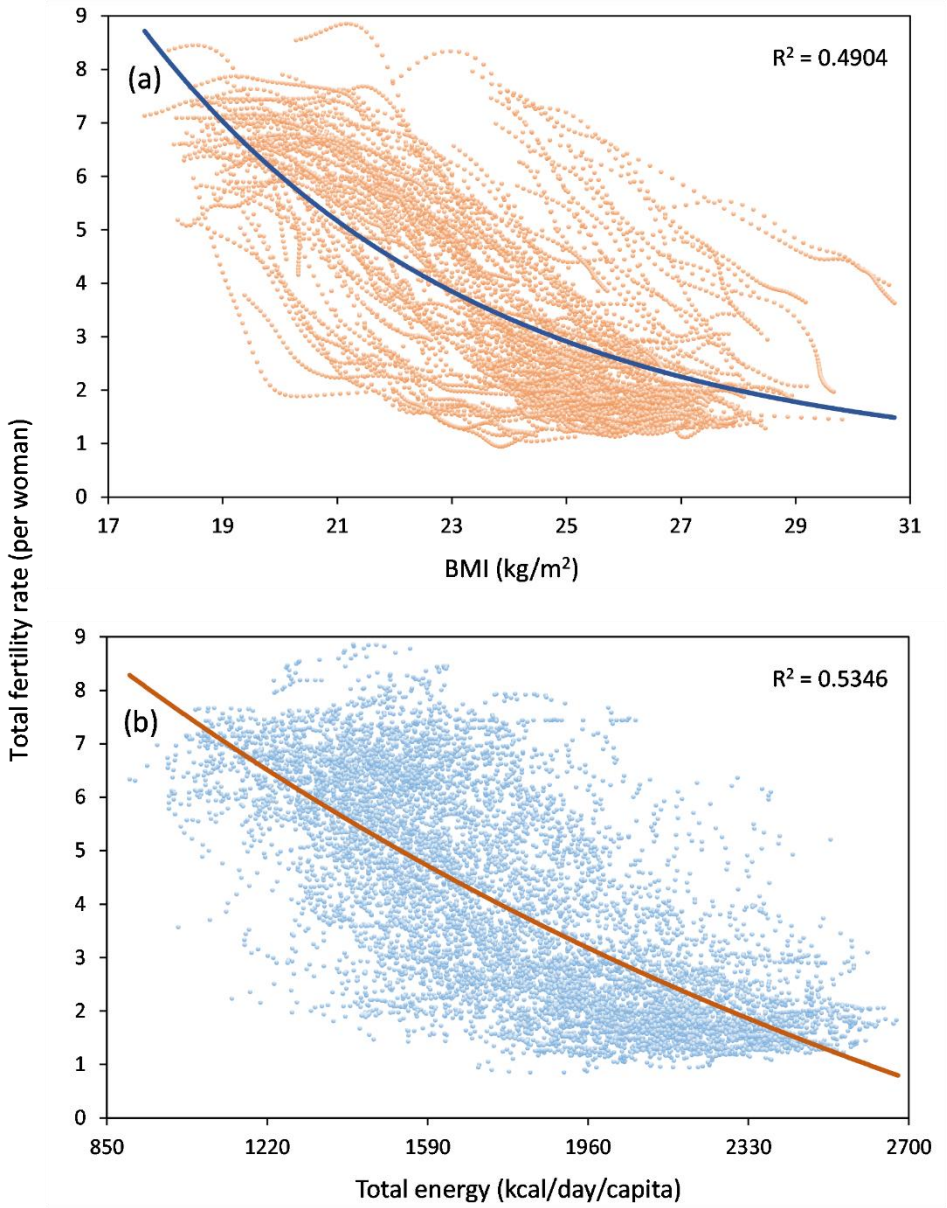

Fig. 6 Aspects of nutrition transition (increasing BMI and total energy availability) correlated against fertility rates. Data cover 1975-2016 (a) and 1961-2019 (b) in 185 countries, with trendlines (both, $p < 0.0001$) produced using a general exponential model ($y = a + b \cdot e^{(c \cdot x)}$), fit with an iterative least squares procedure utilizing the *nls()* function in the *stats* package in R. Pseudo R^2 values calculated using: 1 – { (residual sum of squares) / (total sum of squares) } [401–403]. Food availability data loss-adjusted using 2010 US Department of Agriculture total loss rate (31%) [163]. Data from United Nations (fertility rate and energy availability) [82, 143, 144] and NCD Risk Factor Collaboration (BMI) [83, 386]

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