Environmental Endocrinology

Content

Introduction

The incidence rates of several non-communicable diseases are increasing globally. These include hormone-related metabolic, immunological, and neurological conditions, reproductive disorders, as well as certain

cancers. Adverse secular trends in hormone-regulated biological processes such as the timing of pubertal onset,[1,2] semen quality,[3] and body composition[4,5] have also been documented.

These secular changes have occurred over just a few generations, a time frame much too short to imply genetic changes. This rather indicates that environmental and/or lifestyle factors are involved. Indeed, over the same period significant environmental and lifestyle changes have occurred, which have largely been driven by increased use of fossil resources as fuels but also as building blocks of modern chemicals. Thus, over the last 100 years estimated more than 350,000 new manufactured chemicals have been developed, of which thousands are today produced and marketed on a large scale.[6] This chemical expansion has contributed to significant economic growth and prosperity in developed countries, streamlined food production, and the development of new medicines. However, many of the chemicals used often end up in our bodies.[7,8] This concerns not only chemicals but also anthropogenic air particles, nanoparticles, and microplastics; several of which are shown to be carcinogenic or affect our hormone and immune systems, metabolism, or brain development[9].

The health consequences of these fundamental changes to our environment have become increasingly apparent, but the full extent is far from being properly elucidated. The “One Health theory” describes the interconnections among human, animal, environmental health, and the exposome (i.e. the overall exposure to the environment in a lifespan) and helps understand how, among others, climate change, air, water, and food pollution, and endocrine disrupting chemicals influence endocrine health from conception to death and the well-being of future generations.[10,11] Importantly, since the causes are anthropogenic, there is also great potential to reduce the health consequences of environmental influences through increased awareness, regulation, and prevention.[12] In 2020, the EU launched the ambitious "Chemicals Strategy for Sustainability towards a Non-Toxic Environment".[13] If the strategy's ambitions to protect the population from the most harmful environmental impacts are to be realized, there is a need to strengthen research. Targeted preventive efforts require the necessary knowledge of how different environmental factors impact human health. Considering the endocrine aspects of many non-communicable diseases, this includes an increased understanding of how environmental factors affect hormone systems.

Endocrine disruption by chemicals

Over the second half of the 20th century increasing numbers of reports emerged describing the impact of environmental chemicals on wildlife and human health. These early reports particularly involved reproductive and developmental functions and pointed to disturbed hormonal regulation. Accordingly the term “endocrine disruptors” was proposed at an international workshop in 1992.[14] Even so, the impact of endocrine disrupting chemicals (EDCs) on wildlife and human health was largely underestimated until several reports were published around the turn of the century, which extended the awareness of the problem beyond the scientific community.[15-17] A decade later the World Health Organization/United Nations Environment Program (WHO/UNEP) and the Endocrine Society published pioneering scientific statements on Endocrine Disrupting Chemicals.[18,19] Recently, the European Society of Endocrinology in a position paper also raised concern of endocrine health consequences of human exposures to EDCs.[20]

A first definition of an Endocrine Disrupting Chemical was provided by WHO and the International Programme on Chemical Safety (IPCS) in a report in 2002: “An endocrine disruptor is an exogenous substance

or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations".[15] This definition has more recently been adopted by the European Commission.[21] IPCS also proposed a definition for a potential endocrine disruptor requiring a lower level of evidence: "A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations".[15]

The issue of causation vs correlation. From epidemiology to translational medicine.

There is robust evidence showing the detrimental effects of EDCs in different wildlife species and a large amount of data from experimental cellular and animal models confirms that several environmental chemicals have disrupting action on multiple endocrine systems. Since the beginning, however, the evidence supporting a cause-effect relationship in humans was considered weak and inconclusive largely because most human data derive from epidemiological/association studies, which cannot demonstrate cause-effect relationships. Furthermore, some factors complicate the advancement of knowledge in humans: a) human exposure is generally to a mixture of many EDCs rather than single substances; b) exposures may vary throughout life; c) effects of EDCs are often sex and developmental stage (age) dependent; d) EDCs often don't exert their biological effects in a clear linear dose-response relationship; e) EDCs may have transgenerational effects. However, most likely EDCs will adversely affect humans as demonstrated in many other species, considering the high evolutionary conservation of basic components and mechanisms of hormone actions across species. Notably, the rapid increase in the incidence of certain hormone-related diseases in specific geographical areas indicated that environmental factors play a key role in the pathogenesis. Epidemiology has indeed played a major role in showing the close relationship between exposure to EDCs and certain diseases and malformations.[22,23]The pioneering work of Niels Skakkebæk and collaborators led to the definition of testicular dysgenesis syndrome, which included cryptorchidism, hypospadias, impaired spermatogenesis, and testicular cancer, caused by endocrine disruption *in utero,* potentially as a consequence of prenatal exposure to EDCs, such as pesticides and phthalates.[24,25] A major breakthrough in this field has recently come from the publication of a longitudinal study reporting adverse neurodevelopmental outcomes in a large mother-child cohort exposed to a mixture of EDCs.[26] This study, for the first time, integrated experimental and epidemiological evidence demonstrating a clear risk of language delay, a hallmark of neurodevelop-mental delay, in the offspring of mothers exposed to EDCs during pregnancy.

Characteristics and actions of EDCs

The US Environment Protection Agency has identified more than 1800 chemicals, which can affect endocrine and non-endocrine pathways.[27] In the EU around 100 chemicals have been identified and legally classified as endocrine disruptors.[28] Most known EDCs are organic compounds often composed of cyclic structures, which they have in common with natural steroid- and thyroid hormones. This may explain why some EDCs can mimic the interaction of natural hormones with steroid or thyroid hormone receptors. However, many EDCs have different molecular structures. For instance, per-and polyfluoroalkyl substances (PFAS), a large class of more than 15.000 synthetic chemicals, consist of a fully or partially fluorinated carbon chain, which makes it stable and difficult to degrade, carrying diverse functional groups, such as carboxyl and sulfonate groups. Ultimately, depending on the chemical, endocrine disrupting action may be exerted via a wide series of pathways highly conserved in wildlife and humans. These include receptor and signalling systems for small

molecule hormones (comprising nuclear and non-nuclear hormone receptors and orphan receptors), enzymatic pathways and proteins involved in hormone biosynthesis, transport, or metabolism, as well as neurotransmitter receptors and numerous other mechanisms involved in the regulation and signalling of the endocrine system.[29] EDCs, which exert their action through binding to hormone receptors can act either as agonists, partial agonists, or antagonists of hormonal action and thereby disrupt homeostasis. The major EDC families include a) pharmaceuticals such as trenbolone acetate, ethinylestradiol, dexamethasone, levonorgestrel, rosiglitazone, and metformin; b) cosmetics and personal care products such as phthalates, benzophenones, parabens, triclosan, and diethyl(meta)toluamide (DEET); c) pesticides, herbicides, fungicides such as chlorpyrifos, glyphosate, pyraclostrobin, dichlordiphenyltrichlorethan (DDT), and atrazine; d) industrial chemicals such as bisphenols, polychlorinated biphenyls (PCBs), triphenyl phosphate, per- and polyfluoroalkyl substances (PFAS) such as perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), polybrominated diphenyl ethers (PBDEs), and organotins; e) metals such as lead, cadmium, mercury, and arsenic.

EDCs can be subdivided into persistent and non-persistent substances, with persistent compounds having long elimination half-lives (may be several years or decades) resulting in bioaccumulation, while non-persistent substances can be cleared within hours or days. However, even exposure to non-persistent substances may be (semi-)persistent if the exposure and thereby uptake is frequent/constant. Exposure occurs through food, drinking water, air, soil, food packaging, cosmetics, toys, furniture, and household products. EDCs may be transferred from the mother to her child across the placenta and through breast milk.

Exposure to EDCs and child health

Exposure to EDCs can affect multiple organs and systems in experimental models and wildlife. In humans, the list of diseases linked to EDC exposure is rapidly growing. Exposure to EDCs during critical developmental windows (i.e., foetal life, early postnatal life, and puberty) may permanently affect organ development and function with long-term consequences on health.

Exposure to PBDEs has been related to reduced IQ and intellectual disability, altered timing of puberty, cryptorchidism and testicular cancer. Pesticide exposure has been linked to reduced IQ, intellectual disability, obesity, Type 2 diabetes, prostate cancer, cryptorchidism and hypospadias. BPA may induce obesity, impaired semen quality and testicular dysgenesis syndrome. PFAS exposure has been associated with obesity, increased cholesterol levels, polycystic ovarian syndrome, impaired semen quality, breast cancer, impaired antibody response to immunization, reduced birth weight, kidney, testicular and prostate cancer. Phthalates are involved in early/precocious puberty in girls, male infertility, testicular dysgenesis syndrome and childhood growth failure. Finally, the exposure to EDC mixtures may lead to attention deficit disorder, autism spectrum disorder, impaired neurodevelopment and cryptorchidism.

Impact of EDC exposure on different endocrine functions

Hypothalamic and pituitary function

Few data, mainly derived from cell and animal models, exist on the hypothalamic and pituitary effects of EDCs. There is evidence showing that EDCs affect the hypothalamic expression of GnRH and kisspeptin, influence the pulsatile release of GnRH, and alter pituitary gonadotropin.[30] In particular, GnRH neurons in the preoptic area are targeted by PCBs, DDT (and its metabolites), PBDEs, and 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). Kisspeptin neurons in the anteroventral periventricular nucleus are targeted by PCBs and PFAS/PFOA. KNDy neurons in the arcuate nucleus are targeted by organophosphate flame retardants (OPFRs), PBDEs, PFAS, and TCDD. Pituitary gonadotropes are targeted by PCBs, DDT (and its metabolites), methoxychlor (MXC), PCBs, PFA,S and TCDD. The detrimental effects of EDCs in the hypothalamus occur at low concentrations and ultimately lead to disruption of steroidogenesis, estrous cyclicity, and the onset of puberty. These data, mainly derived from rodents, prompt to investigate whether chronic exposures to EDCs in humans affect fertility with significant implications for public health.

Hypothalamus-pituitary-adrenal axis (HPA) is another target of EDCs. Studies in rodents show an effect of Bisphenol A (BPA), PFOS, tributyltin (TBT), and phthalates on CRH and ACTH production.[31,32] (Pötzl B et al. Endocrine Disruptors: Focus on ...Horm Metab Res 2024; 56: 78–90). EDCs may also exert epigenetic effects in the hypothalamus. The exposure of mice to a mixture of phthalates, pesticides and BPA increases active coping during swimming stress in both sexes, increases locomotion and reduces social interaction in male progeny. This exposure is able to modify the expression of corticosterone receptors, their regulator Fkbp5, corticotropin releasing hormone and its receptor, oxytocin and its receptor, estrogen receptor beta, serotonin receptors (Htr1a, Htr2a) and glutamate receptor subunit Grin2b, in the limbic system of adult animals[33].[33] In rats, the exposure to BPA increases DNA methylation of Fkbp5 and reduces the protein levels in the hippocampus.[34] The BPA effect on Fkbp5 is abolished upon knock-down of ERβ, suggesting a role for this receptor in mediating BPA effects on Fkbp5. Finally, by targeting basal and stress-reactive HPA activity, EDC exposure has been associated with the development of stress-related disorders.[35]

GH and prolactin secretion may be affected by exposure to EDCs. DDT affects the expression of GH and PRL genes in the rainbow trout pituitary.[36] DDT acts as a xenoestrogen, although its potency is much lower than that of estradiol, it is able to increase GH and PRL mRNA at concentrations about 500-fold higher than that of estradiol.

Overall, the available data, generated by studies in experimental models, support the concept that hypothalamus and pituitary are potential targets of the disrupting action of EDCs especially if exposure occurs in early life. Intrauterine programming of the hypothalamus and pituitary is regulated by different environmental influences such as maternal nutrition, oxygenation and stress. There is now compelling experimental evidence that fetal exposure to EDCs play a role in programming and affect the development of these structures leading to a spectrum of endocrine disorders throughout life. The evidence in humans is still scanty for the objective difficulties to obtain long-term epidemiological data and set up controlled studies but the available experimental data prompt to intensify research on the effects of environment on hypothalamus and pituitary organogenesis and function.

Puberty

Female reproduction

Male reproduction

Cryptorchidism, hypospadias, testicular germ cell cancer, and poor semen quality have a common origin in fetal life.[37] This hypothesis of a testicular dysgenesis syndrome has now been extended to also include short anogenital distance (AGD) and impaired testosterone production. Exposure to EDCs, especially during fetal life, may disturb testicular development with lifelong consequences as early reproductive development is linked with adult testis function.[38] Some EDCs also result in fetal growth restriction, which itself is a risk factor for male reproductive disorders. Overall, small study sizes, the large biological variability in reproductive health measures, differences in matrices used for measurement of EDCs, and in particular the difficulty in assessing exposure mixtures often complicate human studies.

Some, but not all, studies have shown associations between cryptorchidism or hypospadias and local use of pesticides, parental occupation in farming or gardening, parental occupational exposure to pesticides[39-42] as well as significant differences in exposure levels between cases and controls, i.e. pesticides, dioxins, flame retardants, phthalates and other EDCs, others have not found this.

The prevalence of testicular cancer, the most common cancer in young men, is increasing in many countries.[43] Association studies with EDC exposure measurements suggest overall a stronger correlation to maternal exposure,[44] i.e. exposure of the young man in fetal life, than to concurrent exposure levels in the young man himself,[40,45] which is in line with the testicular dysgenesis syndrome hypothesis.

The decline of semen quality observed in many countries[3] has stimulated research into potential environmental causes. Studies of prenatal and early life exposures to EDCs are rare but suggest associations of some persistent and non-persistent EDCs with semen quality.[42,46] Meta-analyses of adult exposures to non-persistent chemicals, i.e. phthalates, parabens, BPA, or benzophenones, or persistent chemicals, i.e. PCBs, PFASs and organochlorine pesticides, have shown conflicting results.[46]

AGD, i.e. the distance between the anus and scrotum or ventral base of the penis, is considered a read-out of androgen action in utero.[47] Studies with individual chemicals such as PCBs, dioxins, PBDEs, pesticides, parabens, phenols and PFAS have shown negative associations with anogenital length in male offspring,[42] and a meta-analysis reported a significant reduction in AGD with prenatal phthalate exposure.[48] Interestingly, adult male AGD is in several studies positively associated with sperm parameters.[49-51]

Very few studies exist exploring the effect of EDCs on reproductive hormone levels. Maternal exposure to phthalates, PFOA and dioxins as well as adult exposures to some EDCs have shown effects on the Leydig cell or Sertoli cell axis,[42] but more studies are needed.

Thyroid hormone function

The thyroid gland and the complex thyroid hormone (TH) feedback system are among the known relevant target structures of adverse effects of EDCs. TH regulate human development, growth, anabolic and catabolic processes, as well as maintenance of metabolic homeostasis throughout all life phases. Adequate maternal TH supply is crucial for the healthy development of the human offspring, especially during the first trimester of pregnancy, when the fetal TH system has not yet developed, but also later on during further pregnancy,

fetal development and lactation. Thus, ubiquitous EDC exposure[52] during these and subsequent sensitive windows of development, especially of the central nervous system, jeopardizes health during later life. Yet, more than half of the global population, especially females in their reproductive age, have an insufficient nutritional iodide intake.[53] However, this is essential for maintaining adequate TH synthesis during pregnancy, where demands for the maternal-fetal unit increase. Additional nutritional and environmental exposure to EDC mixtures, targeting the TH system (THS) during this sensitive period already challenged by iodide deficiency, may trigger or even amplify adverse developmental outcomes.[54,55]

Recent progress in TH research revealed that not only the TH producing gland and its key proteins involved in iodide uptake, oxidation, TH biosynthesis, storage and secretion, which has been in the focus of classical (embryo-)toxicology, are affected by EDC exposure. Rather, the systemic aspects of TH distribution, cellular uptake and metabolism as well as receptor mediated T3 action at the local target organ levels, especially in the brain, play a more important role as target structures of EDC interference than the gland itself.

Various classes of known and suspected EDC are known to adversely interfere with the THS, especially during pregnancy and adolescence (see table xx ?), but observational and epidemiological evidence provided by regional and world-wide investigations remains still controversial. Studies have been performed mainly on single EDC compounds (e.g., BPA) or chemical groups (e.g., PFAS, phthalates) but rarely covering complex EDC mixtures, which represent realistic exposure scenarios throughout life. Furthermore, mainly single time point analysis of EDC exposure and/or endpoint/outcome/biomarker parameters have been performed, while only few larger epidemiologic studies include multiple time point analyses of exposure associated with outcome parameters. The majority of publications report on (retrospective, observational) studies with small case numbers or too short monitoring and follow-up periods.

Only recently, first well controlled, sufficiently large populated, prospective and long-term monitoring and assessment studies have been published with statistical power which allows plausible interpretations and strong conclusions. These reports can directly relate epidemiologic human observations to clear cause-effect analyses from meaningful, unequivocal animal model and cellular mechanistic in vitro studies. Extensive results are now available on the effects of pre- and postnatal EDC exposure to the THS (recently reviewed in several meta-analyses[56,57]. Prenatally elevated PFAS (and organochlorine compound) exposure was negatively associated with decreased blood concentrations of fetal total T4.[56] In an adult population, PFAS and PFOA elevations in the blood were negatively associated with total T4, while PFOS concentration was positively associated with free T4 and TSH and negatively associated with total T3 in a subgroup of the populations studied. (Kim 23). Not all studies evaluated in these meta-analyses revealed congruent results. Increasing exposure to PFAS has also been shown to increase plasma T4 concentration and to result in altered amino acid and lipid metabolism in exposed adolescent and young individuals in a recent metabolomic study.[58] Specific exposure dose-response relationships were observed in various subpopulations between some PFAS species and thyroid hormone concentration patterns.[52]

Prenatal exposure to pesticides (e.g., β-HCH and mecarbam) was associated with disruptions of the THS and intermediary metabolism as well as with adverse outcome, such as decreased birth weight.[59] Studies on widely abundant classical and novel phthalate species report on associations between exposure to several phthalates and their metabolites with disturbed function of the hypothalamus-pituitary-thyroid (HPT) axis

during various life phases.[60] Reported data on associations of prenatal exposure to triclosan, an antimicrobial EDC contained in many consumer products for daily body care, and the maternal-fetal THS remain inconclusive.[61]

These recent surveys complement previous scenarios[62] and support data that exposure to various persistent organic pollutants (POPs) and EDCs during the early pregnancy and the perinatal phase perturb the fetal THS, as indicated by altered serum free T4 or total T4 - irrespective of an expected but not observed adequate TSH change. The consequences are negative impact on fetal brain development, IQ and intellectual functions.

These comprehensive assessments for multiple EDC species also complement early data sets on the adverse effects of increased exposure during pregnancy to perchlorate, nitrate, thiocyanate, known antithyroid agents contained in nutritive components, including drinking water or tobacco smoke.[63] Similarly, heavy metals (Hg, PB, Cd) are well known to adversely interfere with the thyroid gland and the THS in the general population. However, crucial measures to control and reduce heavy metal exposure, which adversely affect the THS[64], are already in force and effective and may result in better protection of the thyroid, especially if nutritional supply with iodide is improved in combination with selenium compounds, which inactivate heavy metals.[65]

Meanwhile, strong evidence has accumulated that air pollution, resulting in enhanced exposure to nano- and micro-sized particulate matter (PM), and the toxic gases NO2, SO2 and CO, are adversely associated with various serum parameters reflecting the function of the THS in pregnant women and the general population.[66] Whether these changes impact on fetal (brain) development and/or TH-dependent bodily functions, an issue of high relevance for public health, remains to be studied, also with respect to the precise identification of the nature of the contributing components and their mode of action.

Overall, reported data on impact of maternal and prenatal EDC exposure on the THS of the offspring are still inconclusive, but strongly indicate adverse EDC effects on the maternal and fetal TH status during pregnancy, brain development in the womb and later in life with consequences on intellectual, behavioral, and locomotor functions of the affected offspring.[67]

Whether chemicals found in amniotic fluid, (cord) blood, fetal tissues, or urine and blood of pregnant women and their offspring exert their adverse effects as EDC, neurotoxins or immune-toxic agents (see BPA) or as a combination of these mechanistic modalities remains to be studied in more detail. This will require (prospective) mother-child cohorts of sufficient group size, longitudinal assessment of (pre-, peri- and postnatal) EDC exposure and (non-invasive) monitoring of meaningful parameters, biomarkers and endpoints sufficiently specific for selected health impact and underlying mechanisms. Of note, studies also need to take into account sexual dimorphic patterns of sensitivity, affectedness and outcome of exposure to EDC and their mixtures. Divergent sensitivities, affectedness and outcomes have been reported for prenatal exposure to specific EDC and endpoints monitored in female and male offspring of exposed mothers.

Furthermore, efforts to improve global iodide supply are of eminent importance to strengthen the protection of the thyroid gland and the entire fine-tuned and closely regulated THS against additional adverse EDC effect. This will require to absolutely guarantee adequate nutritional supply with iodide, the essential trace component of the THS, especially during pregnancy and lactation, development and growth of newborns,

children and adolescents as well as during all later life phases. Optimal iodide supply (together with an adapted selenium and iron intake) will protect the thyroid gland and its life-long hormone production and possibly mitigate or even prevent adverse effects of maternal-fetal as well as adult EDC exposure.

Metabolic functions incl. diabetes and obesity

Beside the robust data from in vitro and animal models showing a clear effect of EDCs on adiposity, there is increasing epidemiological evidence in humans showing an association between the exposure to specific EDCs and the risk of obesity.[68] Some EDCs are able to alter regulation of energy balance and promote adiposity ("obesogens"), exerting their action by disrupting peroxisome proliferator-activated receptors, retinoic acid receptors, estrogen receptors, thyroid hormone receptors, adipocyte proliferation and differentiation and central regulation of appetite and satiety.[69]

According to the developmental origins of health and disease hypothesis, fetal and early postnatal life exposure to EDCs may increase the risk of obesity and associated non-communicable diseases in adulthood. Obesogen exposures during development can induce epigenetic changes that persist across generations through the process of transgenerational epigenetic inheritance. The so far recognized environmental chemical obesogens are listed in Table 2. One of the most well-characterized obesogen is the organotin tributyltin (TBT). Organotins are widely used in industry and to some extent in agriculture. Human exposure to organotins can occur via the diet such as seafood contaminated by TBT used in marine shipping applications, or as fungicides for paper mills and industrial water systems. TBT binds to and activates PPARγ and RXR, promoting adipogenesis and lipid accumulation. Other EDC families closely associated with obesity risk are PFAS, phthalates and bisphenols.[70] The exposure to both long- and short-chain PFAS is associated with childhood obesity, though with sexual dimorphism.[71]

Prenatal and childhood exposure to phthalates has also been associated with weight and BMI in girls.[72,73] With regard to bisphenols conflicting data are available.[74,75] Recently, a case control study has shown that a higher exposure to bisphenol-A is associated with the risk of obesity in girls.[76] This finding is consistent with the results of a survey on 1,860 children aged 8–19 years who participated in the 2003–2006 National Health and Nutrition Examination Survey (NHANES). This study had complete data on both urinary BPA concentration and body composition measured by dual-energy X-ray absorptiometry and showed that higher BPA levels were associated with increased fat mass in girls but not in boys.[77]

In exploring the impact of EDCs on obesity risk, it has to be considered that, as humans are exposed to many different EDCs, there is a need to evaluate the mixture effect in addition to the effects induced by single compounds but data on EDC mixtures are still scant.[78]

The overall effect size of the EDC obesogenic action is not negligible and it is comparable with familial and dietary influences.[79] However, compared with sugar-sweetened beverages or snack foods, EDCs are invisible and potentially obesogenic in relatively small quantities, particularly in specific time windows of development. Therefore, minimization of EDC exposure should be included in obesity prevention policies and policy-makers are urged to pay greater attention to EDCs in the development of strategies to reduce obesity prevalence. Furthermore, the transgenerational effects of most EDCs also predispose future generations to undesirable phenotypic traits and diseases, including obesity and related metabolic disorders. Finally, longitudinal observational studies from conception to young adulthood are needed to investigate the long-

term effects of the exposure to single chemicals or mixture of EDCs on obesity risk. These studies should be actively promoted and supported by health and research agencies as the incidence of obesity is increasing worldwide in both childhood and adulthood with the consequent increase of comorbidities including metabolic disorders, cardiovascular disease and cancer.

The list of obesogens includes a) general chemicals such as air pollution and fine particulate matter, Microplastics, PFAS (Per- and poly-fluoroalkyl substances), flame retardants (PBDEs (Polybrominated diphenol ether) and OPFRs (Organophosphate flame retardants)), and PCBs (Dioxins and polychlorinated biphenyls); b) pesticides, biocides and agricultural chemicals such as DDT, tributylin, chlorpyrifos Diazinon, neonicotinoid pesticides, permethrin and tolyfluanid; c) Plastic components and plasticisers such as bisphenols (bisphenol A, S, F and AF), phthalates (DEHP, DBP, DISBP, BBzP) and dibutylin;d) heavy metals such as arsenic and cadmium; e) Food preservatives/additives such as parabens, benzoates, propionic acid, CMC (Carboxymethylcellulose), MSG (Monosodium glutamate), DOSS (Dioctyl Sodium Sulfosuccinate) and 3-BHA (3-tertbutyl-hydroxyanisole).

Calcium homeostasis and bone metabolism

The available scientific evidence shows that exposure to EDCs can affect negatively both bone growth and composition as this is largely a hormone-dependent process. Findings are currently often preliminary and in depth and consolidator studies and complete understanding are yet lacking. Gender effects are suggested with some data being contradictory.[80] Studies have addressed the effects of single EDCs through in vitro and in vivo studies and overall skeletal growth and remodeling processes are affected.[81] Interstitial epiphyseal growth (bone elongation) and appositional growth (bone remodeling) are both required for bone growth,[82] and any disruption of these processes leads to changes in bone strength, plasticity, bending force, architecture, mineral density (BMD) and mineral content (BMC).[80]

Epidemiological studies in humans are yet scarce and have limitations, however, exposure to DDTs, and phthalates has been shown to be associated with changes in the methylation status of both the H19 and IGF2 genes that are well known to be related with Silver Russell and Beckwith Wiedemann's syndromes characterized by reduced and over- growth, respectively.[83] Similar findings were reported in relationship with phthalate exposure, in the ELEMENT study.[84] The CHECK study found a positive association between the DDT metabolite p,p'-DDE, PCB, and Σ19-organochlorine pesticides (Σ19OCPs) exposures and IGF2 methylation status in the placenta, no associations and another placental marker of methylation, LINE-1, and with reduced birth length.[83] PCDD/Fs exposure levels at 2 and 5 years of age would have different effects on height in males with respect to females, showing reduced height at 2 years of age in females only, and an association of exposure levels with increased T3 and IGF-1 levels, again more evident in females than in males.[85] However, these data remained unconfirmed in a later study.[86] Considering the effects of exposure to phthalates, it is generally recognized that the effect of mixtures is worse than that of a single metabolite, and that some of the negative effects on longitudinal growth are mediated by a reduction in IGF-I and IGFBP-3 in the circulation.[87] A 20-year-long study described weak relationships between exposure to phthalates and height z-score during childhood.[88] As for other EDCs, some of the effects of phthalates on logitudinal growth are mediated through changes in BMI.[89]

BPA exposure was described to be associated with down-regulation of IGF-1 and IGF-1R mRNA expression in the embryo with subsequent changes in fetal weight,[90] and other effects would be mediated indirectly by changes in the BMI, due to the negative effects of BPA on bone marrow adipose tissue with subsequent increase in adiposity; this latter is associated with significant clinical effects on bone density and strength.[91] One study reported that high maternal BPS urine concentrations were associated with an increased head circumference and higher birth weight if exposure occurred mainly during the first trimester of pregnancy.[92] Furthermore, reduced BMD was reported at 10 years of age following exposure during pregnancy.[93]

A cross-sectional study in 2292 children, aged 6–9 years, found that exposure to PFAS was associated with lower levels of IGF-1 and sex hormones, thus, likely affecting growth.[94] One of the most recent studies, the HOME study, reported that exposure to PFAS was related with a lower birth weight but at 2 years of age instead increased growth was observed,[95] and PFAS were hypothesized to induce a rapid growth.[96] The NHANES Project Viva and other studies have reported that prenatal and early postnatal PFAS serum levels are associated with reduced BMD in adolescents.[97-100] Polycyclic aromatic hydrocarbons (PAHs) have also negative effects on fetal growth.[101-103]

Summarizing, the studies available in humans point out that exposure to EDCs contributes to growth retardation, delayed ossification, changes in bone length and size, and in bone geometry with subsequent reduction of bone mineral density and quality.

Finally, there are a good number of in vitro and in vivo studies that have identified the affected molecular pathways disrupting bone homeostasis and architecture, including negative effects on the estrogen receptors, disruption of androgen action, induction of apoptosis and modification in differentiation pathways, reduction in IGF-1 type 1 receptor gene expression, changes of the IGF system peptides, and changes in epigenetics in bone cells[80].

Adrenal function

The adrenal gland belongs to the hypothalamic-pituitary-adrenal (HPA) axis and plays a key role in electrolyte homeostasis, stress response and steroidogenesis. It has been long known that the adrenal gland, particularly the cortex, is highly susceptible to exogenous noxa[1] owe to anatomical and histological features[1,2] including increased vascularisation, which allows prompt distribution of produced hormones. However, this makes the adrenal gland available to exogenous substances present in the bloodstream, including EDCs. Furthermore, the lipophilic nature of the cortical cells and the well-developed apparatus for lipid-components uptake, represents an ideal pool for lipid chemical accumulation. Indeed, studies in animal models i.e. rats and mice, showed that certain chemicals accumulate in the adrenal cortex and can cause toxicity.3,4 The cortex also represents an environment for steroidogenesis, during which hydroxylation reactions produces reactive oxidative species (ROS) inducing oxidative stress. Some EDCs, including BPA5, phthalates6 and parabens7, have been described to induce oxidative stress, and exposure to these could potentially further increase ROS hence disrupt the redox balance and negatively affect adrenal function. In one study in Wistar rats, BPA was confirmed to increase oxidative stress and cause other structural changes, with a final increase in corticosterone and adrenocorticotropic hormone (ACTH) levels.8 In addition, some EDCs have been shown to interfere also with hormone distribution and binding to the receptors of target cells. For instance, Shaikh et al. conducted two in silico studies: in the first it was demonstrated that alternative plasticizers di(2-

ethylhexyl)terephthalate (DEHT), tris(2-ethylhexyl) trimellitate (TOTM), and diisononyl hexahydrophthalate (DINCH) can bind to sex-hormone binding globulin (SHBG)9 and in the second study phthalates were predicted to bind to corticosteroid-binding globulin10, suggesting possible changes in physiological distribution of hormones secreted by the adrenal cortex. In a cross-sectional study using the National Health and Nutrition Examination Survey (NHANES) data pesticide p,p'-DDT exposure was associated with lower SHBG levels.11 Additionally, it was found that hexaconazole, a fungicide, could also bind SHBG.12 Furthermore, the HPA axis, can be impaired by factors affecting both the hypothalamus and pituitary gland. Chen and collaborators performed two in vivo studies in pregnant rats showing that exposure to BPA led to increased corticosterone, ACTH and corticotropin releasing hormone secretion with subsequent depressive-like symptoms in the female offsprings13. Additionally, in humans, in a randomized, double-blind crossover trial, it was shown that exposure to particulate matter 2.5 (PM 2.5) led to a substantial rise in cortisol, cortisone and catecholamine levels.14 In contrast, another EDC, PFOS led to suppression of glucocorticoid levels.15 This could be attributed to the blocking effect of this EDC on specific enzymes required for steroid hormone production.16 Interestingly, PFOS was associated also with elevated dehydroepiandrosterone (DHEA), particularly in female rats, in addition to a decreased cortisol/DHEA ratio, suggesting that PFOS were favoring androgen production.15 These changes suggest a crosstalk between EDC-mediated impaired adrenocortical function and potential female reproductive disorders, as PCOS, which is associated with increased DHEA levels.17 Pharmaceutical drugs, represent a major EDC family, having the potential to disrupt adrenal function, by directly affecting the adrenals and by dysregulating the hypothalamus and pituitary gland including adrenal insufficiency,18 a life-threatening condition. In Europe, an increased prevalence and a trend to higher incidence of adrenal insufficiency has been observed.19,20 Finally, many in vivo studies have shown that prenatal exposure to DDT can impair adrenal cortex22,23 and medulla organogenesis.24

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Endocrine cancers

Evidence suggesting a role of EDCs in the aetiology and progression of endocrine cancers encompass mechanistic studies, epidemiological findings, and experimental research. EDCs interact with hormonal pathways and disrupt hormone homeostasis, which may promote hyperplasia of hormone producing cells and activation of tumorigenic pathways. They can alter gene expression, induce epigenetic changes,[104] and disrupt cellular and immune function[105], thereby contributing to the development and progression of cancers. EDCs can also influence the tumour microenvironment[106] by affecting immune response, inflammation, and angiogenesis,[107] all of which are critical for cancer development and progression.

Thyroid cancer, which is the most common endocrine malignancy, has seen a global increase in incidence. While this increase is largely due to better diagnosis, it also raising concerns about environmental factors like EDCs.[108] In a recent meta-analysis, exposures to the EDCs PBDEs, phthalates, and heavy metal were associated with increased risk of thyroid cancer, while no significant association were found for BPA.[109] However, this might reflect the innate challenge in epidemiological studies of a high risk of exposure misclassification and low statistical power when studying exposures to non-persistent chemicals with a high day-to-day variation such as BPA.

Only two studies to date have assessed associations between EDC exposure and adrenal tumors in humans. One of these found elevated specific POPs in patients with aldosteronoma.[110] The second, reported increased

BPA levels, particularly in women with nonfunctioning adrenal incidentalomas.[111] However, these studies lack data on specific exposure, including time and doses, highlighting the need for further investigation.

For some endocrine cancers the malignancy may arise secondary to gland dysfunction in which EDCs may play a role e.g. as in pancreatic neuroendocrine tumours. Pancreatic neuroendocrine tumours are rare, but incidence rates are increasing,[112] and known risk factors include smoking and type 2 diabetes. Several EDCs have been associated with increased risk of developing type 2 diabetes.[113] Agents involved in the initiation phase of pancreatic cancers in general include organ-chlorinated compounds and heavy metals; many of which are EDCs.[114]

Cancers of hormone-sensitive tissues such as breast, endometrial, prostate, and testicular germ cell cancers have also been associated with exposure to EDCs suggesting that EDCs may be a risk factor in the development of these tumours.[115-119]

Future research priorities

There is now robust evidence indicating EDCs to be one of the leading environmental risks globally. Such evidence should be further strengthened.

- *In vitro* and *in vivo* mechanistic studies are still needed to uncover or validate new modes of EDC action and biomarkers of endocrine disrupting effects using state-of-the-art methodologies e.g. transcriptomics and epigenetics.
- Epidemiological studies remain crucial to identify/monitor certain hormone-related diseases and conditions in relation to the degree of exposure in different subpopulations or different geographical areas including needs for:
    - follow-up studies to study long-term and transgenerational adverse effects and elucidate underlying pathophysiological mechanisms.
    - longitudinal or repeated cross-sectional population studies to assess trends in exposure and the incidence of specific diseases over time as well as pre- and post-intervention/regulation to monitor the effects of preventive measures.
    - integrating more comprehensive exposure estimates such as human biomonitoring by suspect screening/non-targeted analyses and use of (real-time) spatial exposure measures.
    - integrating -omics methodologies; e.g. transcriptome-wide association studies can aid in dissecting environmental chemical-gene interactions and exposure-associated changes in the metabolome can unveil pathways involved.

Pharmaceuticals

Modern medicine is characterized by a tremendous increase in the number of medications for the treatment of diseases or prevention of long-term disease consequences. Today, there are thousands of products on the market, and pharmaceutical development of novel targeted medications for humans and animals is a large-scale business.[120] Physicians and pharmacists are traditionally trained in the appropriate application of drugs for specific indications. Information about potential side-effects and interactions of medications are also

readily available and their documentation is a legal requirement. However, very few healthcare professionals know that some, even rather common and widely used, medications may have endocrine-disrupting effects. This may occur through the same pathway as its therapeutic application and sometimes through additives, capsules, or medical devices such as i.v. tubes.[121,122] There is also growing concern about pharmaceuticals and their derivatives found in the environment, which can lead to unintended exposure.[123,124] There is still a paucity of data on the extent and health effects of this unintentional exposure.[125]

Worldwide, the production and consumption of prescription medicines as well as over-the-counter drugs increases.[120] An example of this development is the use of mild analgesics.[126] Epidemiological human studies as well as experimental studies indicate that paracetamol and non-steroidal anti-inflammatory drugs (NSAID), i.e. aspirin, diclofenac, and indomethacin, have adverse effects on testis and ovarian development and reproductive function,[127-129] especially on the offspring if taken during pregnancy.[130] Another example is Metformin, a common drug for type 2 diabetes mellitus, for which wildlife and human studies have raised concerns about its broad environmental distribution and anti-androgenic effects on the male reproductive tract.[131] Anti-fungal medications such as the widely used azole compounds affect steroidogenesis,[132,133] which may be of particular concern when taken during sensitive developmental windows such as pregnancy. Immune checkpoint inhibitors, which have emerged as new effective treatments of several types of cancer, can cause both reversible and irreversible endocrine effects.[134] These pharmaceuticals are the most recent example of the importance of understanding common pathways of action in living organisms from a holistic systems biology.

Future research priorities

Research into endocrine-disrupting effects of pharmaceuticals is only at its beginning. However, compared to environmental exposure levels, medications are administered at higher doses per body weight or body surface and often over long periods.

- Research in the environmental fate of pharmaceuticals and in methodologies to prevent environmental contamination due to human use of pharmaceuticals.
- Adverse (side)effects on the endocrine system, including transgenerational effects, should be conducted as part of the safety testing for pharmaceuticals.

Climate

The current climate change, driven by human activities such as burning fossil fuels and deforestation, has far-reaching consequences for health. Rising temperatures, extreme weather events, and changes in disease patterns are current direct and indirect threats. Children are vulnerable to heat-related illnesses due to their higher metabolic rates and lower ability to regulate body temperature. The elderly also represents a vulnerable population.[135] Heatwaves can lead to dehydration, heat exhaustion, and endocrine imbalance besides heatstroke. In a large population study seasonal climatic factors such as temperature, rainfall, aqueous vapour pressure, sunshine hours, and air pollution parameters showed differential effects on thyroid homeostasis.[136] This indirectly has consequences on growth in children and metabolism and cognitive function both in children and adults. Global warming also causes evaporation of iodide from seawater and in

regions distant from the coast resulting in a depletion of iodide in plant foods and drinking water ultimately affecting thyroid function.[137,138]

Nitrate competes with iodide uptake by the thyroid, and has an impact on hormonal synthesis; in addition, some nitrosamines are known carcinogens.[139] Seasonal heavy rains wash away soil minerals, while temperature spikes contribute to elevated nitrate and nitrite concentrations, and cause moisture loss in fruits and vegetables further increasing these levels.[139] Such effects may counteract the altered availability of iodide for thyroid hormone biosynthesis.

Higher outdoor temperatures can favour the obesity pandemic by decreasing the opportunity and motivation for outdoor physical activity. Climate change has also an effect on gene expression patterns, and higher temperatures would determine overall a reduced energy expenditure. This is associated with changes in the amounts of white and brown adipose tissue, with subsequent changes in adipocytokines, among other factors, and would favour the complications arising from obesity.[140]

Future research priorities

A more comprehensive understanding of connections among endocrine diseases, climatic changes, pollution, biodiversity, and food is warranted to pursue the One Health approach.

- Understanding the impact of climatic factors on human health including metabolism, thyroid function, and reproduction is an issue of increasing importance.
- Understanding the impact of climate change on the quality of food products including changes in micronutrients and contaminants and how this relates to health consequences is currently a need.

Air and water pollution

Air pollution is largely driven by the combustion of fossil fuels, greenhouse gases, and industrial processes. Air pollutants such as particulate matter (PM), nitrogen dioxide (NO2), and ozone (O3) have many effects. Many air pollutants carry endocrine disrupting chemicals, such as polycyclic aromatic hydrocarbons, phthalates, mercury, and perchlorate.[141,142]

Fat-soluble airborne contaminants may accumulate in adipose tissue during pregnancy and contribute to preterm birth and low birth weight,[143] and to the increase in non-communicable diseases later in life. Recent research suggests a link between neuroendocrine effects of air pollution and cognitive impairment in children.[144] Oxidative stress damage, inflammation, endocrine disruption, and epigenetic changes are all implicated. Airborne toxins can interfere with thyroid function. Higher exposures to fine particulate matter ≤ 2.5 µm ($PM_{2.5}$) -bound metals have been associated with lower maternal fT4 and fT3 levels, and preconception $PM_{2.5}$ and PM_{10} exposure would increase the risk of hypothyroidism during pregnancy.[145] Furthermore, the elicited inflammatory response and oxidative stress can potentially trigger autoimmune responses against the thyroid gland and worsen asthma symptoms and respiratory conditions.

Moreover, some evidence suggests that $PM_{2.5}$ decreases the number of ovarian follicles in females.[146] Increased incidence and prevalence of type 2 diabetes mellitus have been associated with combined exposure to PM and NO_2.[147] Bone strength seems to be affected too.[148] Overall, studies and epidemiology

data have evidenced a clear association between PM exposure and hormone-related clinical symptoms as well as a number of conditions of multifactorial origin.

Light pollution has also emerged as a health concern in modern societies for its effects on hormonal circadian rhythms. The extensive use of electronic devices as well as artificial light are of concern as they disrupt the natural darkness required for melatonin production. The consequences extend beyond sleep disorders, potentially contributing to a range of health issues, like mood and metabolic disorders.[149] The increase in central precocious puberty during the pandemic has also been related to the huge increase in screen time in children during that period.[150,151]

Drinking water sources can be polluted by heavy metals, environmentally persistent pharmaceutical pollutants, and other endocrine disruptors (e.g., pesticides, pharmaceuticals, herbicides, bisphenols). Most come from waste discharged from industrial activities, such as paper and textile mills, leather industries, and waste water for agricultural purposes.[124] Perchlorate can interfere with iodide uptake by the thyroid gland, leading to thyroid dysfunction. Arsenic contaminated water can favour diabetes affecting insulin signal transduction, secretion and sensitivity, and adipocyte development.[152] Cadmium favours adipocyte hyperplasia and hypertrophy, alters appetite and satiety regulation, and decreases insulin sensitivity.[152]

In conclusion, water pollution also influences the endocrine system in a multifactorial fashion. Depending on the contaminants, several hormone-related conditions and multifactorial diseases are affected.

Future research priorities

Future research should evaluate the prolonged and transgenerational effects of environmental pollution on human health. Longitudinal studies will play a pivotal role in tracking the effects of exposures over time.

- Mapping of pollution and identification of high-exposure locations ("hot-spots") and linking to disease incidences by e.g.:
    - Using Geographic Information Systems (GIS) for geospatial relationships between data on pollution and factors affecting pollution (e.g. traffic, industry, agriculture) and spatial dependent health data (e.g. from health data registries or medical re-imbursement systems).
    - Human geo-sensing approaches to obtain individual exposure profiles for linking to health data.

Stressful environments

Diseases characterized by a very steep and recent increase in incidence such as obesity, cardio-vascular pathologies, fatigue syndrome, anxiety, and auto-immunity are all associated with dysregulated stress response. Stress happens when homeostasis of an organism is threatened. Targets of the stress effectors include the cognitive, reward and fear systems, growth, the hypothalamic-pituitary-adrenal, -gonadal, and -thyroid hormone axes, as well as the control of energy balance.[153] For that reason, any excessive, prolonged, or maladaptive stress response acts as an endocrine disruptor and can impact growth, adiposity, appetite, neurodevelopment, reproduction, or cognitive functions. Stress may also act as a mediator for adverse effects of EDCs, such as phthalates.[154] Stress encompasses several forms including natural and anthropogenic disasters, social or economic difficulties, and malnutrition. Hence, its epidemiology is extremely difficult to

estimate and varies widely with time and along the globe. Notably, epidemiological studies have linked a recent impairment of children and adolescent mental health with increasing educational and economic stressors.[155,156] Stress regulation is programmed during foetal life and recent studies have shown that any disruption during this period leads to long-lasting dysregulation of stress and predisposition to later diseases including neuropsychiatric disorders, cardio-vascular diseases, adiposity, and impaired reproductive health.[157,158] Such observations are consistent with the Developmental Origins of Health and Disease paradigm linking the risk of adult disease with the environmental conditions of early life.[159] Therefore, the continued ability to respond appropriately to stress is a necessary component of disease prevention.[158]

Future research priorities

Major challenges are the definition and evaluation of stress as well as the identification of system-specific endpoints. Future studies should focus on that aspect.

- Strong data now support a sex difference in the regulation and response to stress including early life exposure to stress.[160] Such sex differences should systematically be taken into account when exploring mechanisms of action and consequences of stress as it may depend on hormonal or genetic regulation.
- Rodent models have illustrated the role of the placenta in mediating the effects of gestational stress on neurodevelopment or metabolic health.[161] Studies are needed to elucidate the crosstalk between the placenta and later health in humans and identify relevant placental markers of stress. This might open new avenues for preventing metabolic or neuropsychological diseases in future generations.
- Parental stress occurring before conception leads to alteration of adrenal response to stress as well as impaired psychological health in the descendants and preclinical models suggest that epigenetic modifications of germ cells might explain such transmission.[162] As epigenetic changes in sperm are associated with early life adverse events in men, further studies are required to identify whether such changes lead to specific outcomes in the descendants.

Conclusion

The aetiology and/or manifestation of several non-communicable diseases on the rise often contains an element of hormonal dysregulation. The endocrine system plays a crucial role in regulation of homeostasis within the human body through hormone signalling. In response to external factors, the endocrine system sustains homeostasis by changing internal conditions as required to survive the external challenges. Thus evolutionary, endocrine systems have evolved to cope with natural environmental changes e.g., changes in temperature or differences in resources due to seasonal or climatic variation. However, since the beginning of industrialisation, anthropogenic changes to our environment have accelerated at an unprecedented rate and to the extent that the resilience of endocrine systems is challenged. Understanding the interaction between environmental factors, human exposures, and disease calls for inter-disciplinary collaborations. In this collaboration, clinical and basic endocrinologists can play an important role contributing expert knowledge on the endocrine system including crosstalk between different hormone pathways and the important considerations of sex and different life stages.

Table 1. Examples of known EDCs and related adverse outcomes	
EDC exposure	**Outcome**
Polybrominated diphenyl ethers (PBDEs)	Reduced IQ and intellectual disability, altered timing of puberty, cryptorchidism, testicular cancer
Pesticides	Reduced IQ, intellectual disability, obesity, Type 2 diabetes, prostate cancer, cryptorchidism, hypospadias
Bisphenol A (BPA)	Obesity, impaired semen quality, testicular dysgenesis syndrome
Per-and polyfluoroalkyl substances (PFAS)	Obesity, increased cholesterol levels, polycystic ovarian syndrome, impaired semen quality, breast cancer, impaired antibody response to immunization, reduced birth weight, kidney, testicular and prostate cancer
Phthalates	Early/precocious puberty in girls, male infertility, testicular dysgenesis syndrome, childhood growth
Mixture of EDCs	Attention deficit disorder, autism spectrum disorder, impaired neurodevelopment, cryptorchidism

Table 2. Examples of environmental obesogenic chemicals
General chemicals
Air Pollution and fine particulate matter Microplastics PFAS (Per- and poly-fluoroalkyl substances) Flame retardants, PBDEs (Polybrominated diphenol ether) and OPFRs (Organophosphate flame retardants) PCBs (Dioxins and polychlorinated biphenyls)
Pesticides, biocides incl. agricultural chemicals
DDT Tributylin Chlorpyrifos Diazinon Neonicotinoid pesticides Permethrin Tolyfluanid
Plastic components and plasticisers
Bisphenols (bisphenol A, S, F and AF) Phtathalates (DEHP, DBP, DISBP, BBzP) dibutylin
Heavy metals
Arsenic Cadmium
Food preservatives/additives
Parabens Benzoates Propionic acid CMC (Carboxymethylcellulose) MSG (Monosodium glutamate) DOSS (Dioctyl Sodium Sulfosuccinate) 3-BHA (3-tertbutyl-hydroxyanisole)

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