

Hormones in European Health Policies:

How endocrinologists can contribute towards a healthier Europe



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European Society of Endocrinology White Paper

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Methodology

This paper is based on an extensive consultation with endocrinologists across Europe, combined with expert engagement and desk research.

A large survey carried out in 2018, and in which more than 3,000 endocrine healthcare providers participated, provided the first ever mapping of endocrinology in Europe. The survey included an assessment of future trends and areas where improved efforts – clinical, research and policy – are needed. A second survey was conducted among the National Endocrine Societies that are members of the ESE Council of Affiliated Societies. Forty-three societies provided their views on the importance and needs of endocrine health and diseases in European and national health policies. These surveys were followed up with a careful assessment of European health policies, initially in the summer of 2019, with revisions in 2020 taking the effects of the coronavirus pandemic into consideration.

In-depth interviews with endocrinology experts across various fields contributed to the development of responses to several consultations issued by the European Commission and formed the basis of the policy content of this White Paper. All persons listed under ‘Acknowledgements’ contributed to a certain phase in this process and provided input into the manuscript of the White Paper. In a final phase the White Paper was submitted for final comments and endorsements to experts, the National Endocrine Societies and Specialist Endocrine Societies affiliated with ESE, as well as selected other stakeholders. The White Paper editing process ended on 30 March 2021. Any developments after this date have therefore not been taken into account.

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Introduction

This White Paper will introduce the reader to the importance of hormones in everyday life, and the contributions that the hormone specialist, the endocrinologist, may offer to major European health policies developed or under development by European and national institutions.

Hormones are vital to good human health. Every day they determine our development and growth, how our metabolism handles the food we consume, our sexual function and fertility, and our cognitive processes. Our general well-being is determined by these regulatory substances from the moment of our conception until the day we die. When the hormonal systems become out of balance or fail, prevalent non-communicable diseases with enormous socioeconomic impact like obesity, diabetes, cancer, osteoporosis and infertility develop. Many patients affected by these common diseases are frail and vulnerable as clearly demonstrated by the current COVID-19 pandemic. The effective prevention and treatment of these diseases is the best way to protect these high-risk patients. Many rare diseases can also be connected to failures in our hormone system. Among the many factors that can cause the hormone system to fail, the external environment is more and more recognised as a key driver.

The European Society of Endocrinology (ESE), on behalf of more than 20,000 endocrinologists in Europe as well as the millions of patients with endocrine diseases whom it represents, applauds the agenda of the European Institutions for the period 2019–2024.

The Cancer Mission and Beating Cancer Plan, the Green Deal, the Chemicals Strategy for Sustainability, the EU4Health Strategy and the Healthy Ageing agenda, to mention a few: these plans are highly relevant to our community of endocrine specialists, the science they develop and the patients they see. Our endocrine ‘hormone’ expertise provides relevant insights needed to develop targeted action plans, and support the implementation and impact of these plans, aiming ultimately for better health for citizens around Europe – both inside and outside the EU.

In this document, the community of European endocrine specialists presents its views on how, based on the science we develop, the clinical work we do and our health-related expectations towards the future, the endocrine discipline can contribute to better health in Europe.

The European Society of Endocrinology is grateful to all members and non-members, experts and other societies that worked together with ESE to enable us to present this document. Statements relating to the opinions of the European endocrine community are derived from a large survey, done at the end of 2018, and to which more than 3,000 endocrine professionals (doctors, nurses, scientists, trainees and others) responded.

ESE is committed to supporting the European and national institutions in developing better healthcare policies, to the benefit of all European citizens.



Andrea Giustina

President of the European Society of Endocrinology (2019-2021)

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Executive summary

Endocrinology is the field of medicine that relates to human hormonal systems. The endocrine system plays an important role in the body's ability to maintain fundamental processes for life including heartbeat regulation, bone/tissue structure and growth, energy intake and expenditure, as well as the ability to conceive a baby. Disorders of the endocrine system cause conditions such as diabetes, obesity, atherosclerosis, thyroid disease, growth disorders, hypertension, osteoporosis, infertility and sexual dysfunction, endocrine cancers and a host of other endocrine-related illnesses.¹ Recent research shows that endocrine-related conditions such as obesity, diabetes mellitus and hypovitaminosis D also negatively impact patient outcomes with regard to COVID-19.²

With this White Paper, we call on all policymakers in Europe, including the EU institutions and national governments across Europe, to **recognise the importance of endocrinology** in all EU and national health policies. Addressing this cross-cutting, and in many cases, underlying element is crucial if we want to achieve the objectives set out in key programmes such as the plans to address COVID-19 and other pandemics, national cancer plans, obesity action plans, rare disease networks, chemicals legislation and much more.

The four chapters of this White Paper set out some of the key priority areas linked to endocrinology that are having some of the biggest effects on societal health today. There are many more – the prevention, diagnosis and interdisciplinary care of diabetes, avoiding osteoporosis and ensuring general bone health, vitamin D and iodine deficiencies as well as thyroid health, to name a few. While all endocrine diseases deserve heightened attention, the four areas below are among the most pressing at this point in time.

Obesity and the complex hormonal relationship

Obesity is defined as having abnormal or excessive fat accumulation that presents a risk to health.³ The traditional view of fat tissue (known as adipose tissue) is that it is an inactive reserve for energy storage – when in fact it is an endocrine organ, producing over 600 different hormones.⁴ Adipose tissue is integrally involved in coordinating a variety of biological processes including energy metabolism, neuroendocrine function and immune function.⁵

Obesity increases the risk of comorbidities like type 2 diabetes, hypertension, cardiovascular diseases, depression, infertility and arthritis, and is a contributing factor to a host of life-threatening and debilitating diseases.^{6,7} Obesity is also a risk factor for a number of cancers,⁸ and closely linked to adverse outcomes from COVID-19.⁹

The European Commission's March 2021 dedicated brief on obesity prevention acknowledges the scale of the issue and defines obesity as a 'chronic relapsing disease', which in turn acts as a gateway to a range of other non-communicable diseases, such as diabetes, cardiovascular diseases and cancer.¹⁰ To adequately address this societal challenge, the EU and national governments across Europe should immediately and without further delay **treat obesity as a disease** and recognise **the central role of hormones in preventing, treating and living with overweight and obesity**. In terms of concrete policy opportunities, now is the time to reinforce the 'fork' side of the Farm to Fork Strategy,¹¹ to encourage healthy lifestyle habits and to put appropriate resources behind prevention, treatment and living with obesity. On the 'farm' side, we should reduce exposure to the many plant protection products that contain Endocrine Disrupting Chemicals (EDCs), a contributing factor to obesity.¹² Partnering with scientific societies such as ESE and multi-stakeholder initiatives such as OPEN-EU¹³ would help provide efficient and comprehensive solutions to this massive societal issue.

Rare endocrine disease in Europe

Rare diseases, which affect fewer than 1 in 2,000 people,¹⁴ are less well known and researched, but cover a wide range of conditions. Despite their rarity, these conditions collectively affect approximately 30 million people across Europe¹⁵ and come with particular challenges related to time to diagnosis, innovative treatment options, and investment into research.

European Reference Networks (ERNs) have been instrumental in creating clearly defined structures for sharing knowledge and care coordination for specific rare diseases across the EU. These knowledge-based networks have been critical in shaping the rare disease policy space. However, greater support from the EU is needed to improve their functionality and to improve health outcomes in rare disease patient populations.

To reap the benefits of the ERNs and further improve outcomes for those suffering from rare endocrine diseases, the EU and Member States should continue **evolving and expanding funding for ERNs**. Horizon Europe funding would allow ERNs to expand their activities and create a pan-EU data acquisition strategy to improve current rare disease registries in a common and uniform data space, better coordinate the projects and their infrastructure, and compensate patients and the medical/academic communities for giving their valuable time to the study of these diseases.

National governments should **increase funding for Orphan Medicinal Products** to provide better incentives for the development of medicines for patients with rare (endocrine) diseases and reform their pricing structures to provide incentives to invest in the use of 'old' medicines for new purposes.

At the EU level there is an urgent need to **move forward on European-level Health Technology Assessment (HTA)**¹⁶ legislation and joint funding to make medicines for rare diseases available and accessible in all EU countries.

Cancer and the endocrine system

Cancer is the second leading cause of death and morbidity in Europe, with more than 3.7 million new cases and 1.9 million deaths each year.¹⁷ The interaction between the endocrine system and cancer is complex, and new research has highlighted the intricate nature of this interaction in terms of prevention, treatment and post-treatment care. This manifests itself through endocrine cancers, as well as patient vulnerability to aggressive anti-cancer treatments that result in endocrine comorbidities in cancer survivors. This interaction also relates to obesity as a gateway disease for cancer and other cancer risk factors such as exposure to EDCs.

To address this challenge, the EU and Member States should appropriately focus on and **include the endocrine perspective when implementing the recently published Beating Cancer Plan**¹⁸ and other cancer-related policies, including through making **prevention** measures a focus area, **ensuring that ERNs have a key role** in improving early detection, diagnosis and treatment, encouraging National Action Plans to **address gateway diseases and comorbidities** in cancer survivors and creating **pan-European databases** for major and rarer endocrine-related cancers. Specific and

sufficient attention needs to be directed to the impact of Endocrine Disrupting Chemicals and prevention, treatment and long-term management of obesity, all important and actionable factors in the prevention of cancer.

Through the Horizon Europe Mission Board for Cancer and other funding mechanisms, the EU and national governments should direct future cancer funding towards academic consortia to study evolving epidemiological trends of (endocrine) cancers and improve current diagnostic processes (for example to improve the current late diagnosis of neuroendocrine tumours).

Endocrine Disrupting Chemicals: exposure and health risks

Endocrine Disrupting Chemicals (EDCs) are substances that mimic, block or interfere with hormones in the body's endocrine system. EDCs are found in everyday consumer items including detergents, flame retardants, food additives, children's toys, sunscreen, textiles, anti-bacterial soaps, cosmetics, plastic bottles, metal food cans and pesticides.¹⁹ **Recent studies estimate that EDCs contribute substantially to disease and disability across a person's lifetime, costing hundreds of billions of Euros per year.**²⁰

To safeguard human health and the environment, the European Commission and the European Chemicals Agency (ECHA) should strictly **apply the precautionary principle**, to avoid production, distribution and exposure to pesticides, biocides or consumer products containing suspected EDCs. The European Commission has taken great steps towards phasing out EDCs with its recently published Chemicals Strategy for Sustainability.²¹

The European institutions should implement without delay the many actionable proposals in the Chemicals Strategy for Sustainability and establish a **legally binding hazard identification of EDCs, improving the existing criteria** for plant protection and biocides to lower the burden of proof and allow more harmful substances to be restricted, boost **funding for alternatives** and create a citizen portal to **raise awareness** about the prevalence and harmful effects of EDCs. Other welcome steps include the proposals to provide better public information, to develop a **generic approach to assessing chemicals**, to **register polymers of concern**, and to introduce **risk assessment factors for mixtures** under REACH and assess combination effects in other legislation.



Endocrine health and disorders

Introduction

Endocrinology is the field of medicine that relates to the human endocrine system, a network of cells, tissues and organs that produces and releases hormones into the bloodstream, regulating important bodily functions.

The endocrine system plays an important role in the body's ability to maintain fundamental processes for life including heartbeat regulation, bone/tissue structure and growth, energy intake and expenditure, as well as the ability to conceive a baby. The more well-known hormone-producing glands in the human body include the hypothalamus, the pineal gland, the pituitary gland, the brain, the thyroid and the parathyroid glands, the adrenal gland, the pancreas, the ovaries and the testes.²² However, hormones are also secreted by almost any other tissue in the body such as adipose cells (fat cells), gut, heart, kidney, lung, muscle, skin and bone – all of

which have an important role in the regulation and function of the human body.^{6,23,24,25}

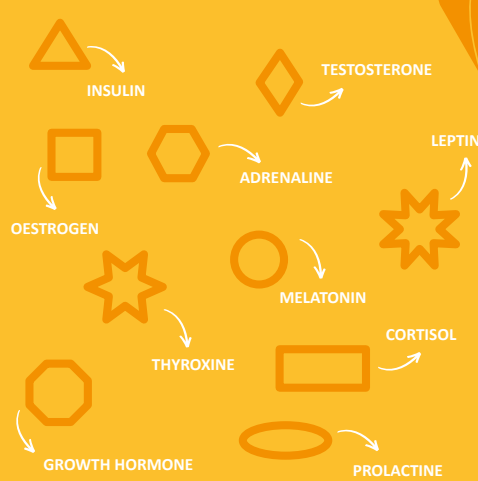
Hormones are critical to health and well-being throughout life. They have a central role in regulating foetal growth and development, maturation of an adolescent into adult life, and other important life-course changes resulting in a fertile and healthy ageing individual.^{26,27}

Figure 1: How hormones work

Hormones are chemical messengers that travel throughout the body, telling our cells and organs what to do.

Endocrinology is the study of hormones.
Hormones are essential for our everyday survival.

There are hundreds of different types of hormones, each with its own essential job.



HORMONES TELL YOU

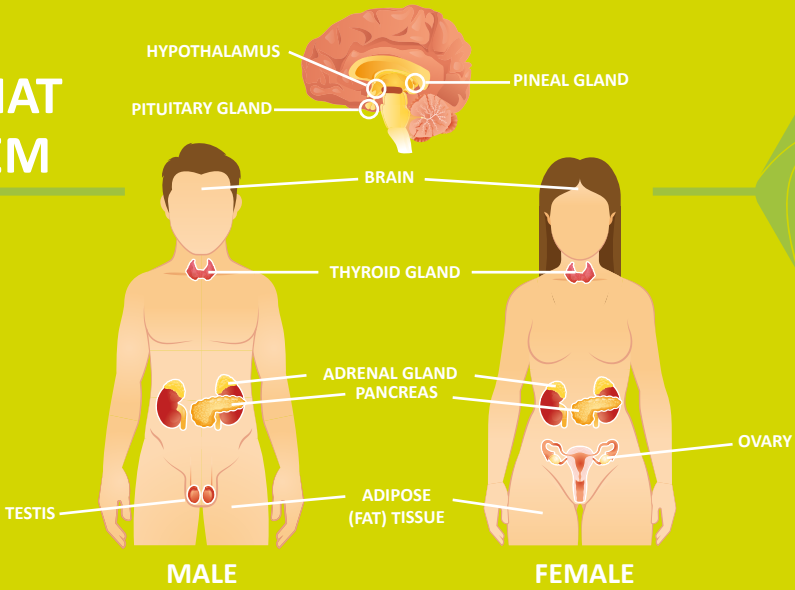


HORMONES HELP YOU



HORMONES COME FROM THE GLANDS AND TISSUES THAT FORM THE ENDOCRINE SYSTEM

The glands secrete hormones to produce specific responses from cells and organs that tell them what to do



Once released, they bind themselves to target receptors that fit the hormone perfectly

Endocrine disorders are amongst the biggest diseases to impact society.

Disorders of the endocrine system cause conditions such as diabetes, obesity, thyroid disease, growth disorders, hypertension, osteoporosis, infertility and sexual dysfunction, and a host of other endocrine-related illnesses.²⁸

“More than three quarters of the population will need an endocrinologist at some point in their life.”



Prof. Dr Uberto Pagotto,
Unit of Endocrinology and Prevention
and Care of Diabetes, Policlinic
S.Orsola, University of Bologna, Italy
ESE Focus Area Lead Diabetes Obesity
Metabolism and Nutrition

A 2018 mapping of more than 3,000 endocrinologists showed the following distribution of workload and disease areas:²⁹

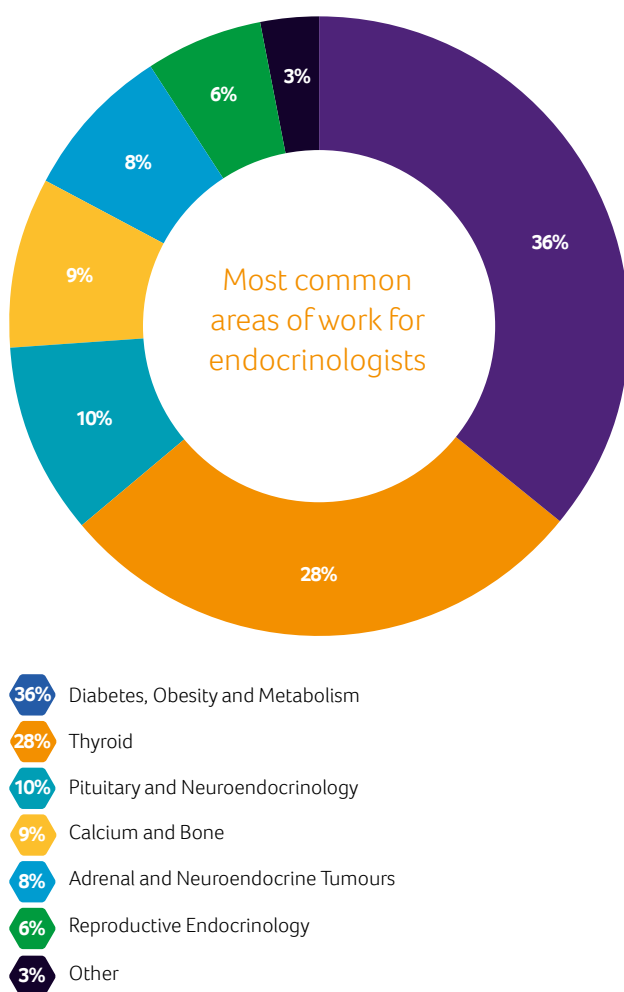


Figure 2: Representation of the most common areas of work for endocrinologist
Data from the Mapping Endocrinology in Europe (MEEnEU) survey carried out by
ESE in 2018.

Today, both the developed and developing world face serious public health challenges caused by the most common endocrine disorders. Diabetes, obesity and thyroid-related diseases are amongst the most prevalent and well-known. On the other hand, endocrine diseases which are uncommon and unfamiliar, like rare disorders of adrenal, pituitary, sexual differentiation, or related to the bone and calcium metabolism, lipid disorders and inborn disorders of metabolism, collectively account for a large proportion of endocrine patients.

As well as direct effects on the regulation of bodily functions, disorders of the endocrine system can lead to cardiovascular comorbidities, cancer and mental health conditions. Hormones also modulate other body systems such as the immune system. The sensitivity and complexity of the endocrine system means that it is also very susceptible to medication, such as aggressive anti-cancer treatments, as well as EDCs present in our environment, which can in turn influence human development as well as both obesity and cancer.³⁰

The link between COVID-19 and endocrine disorders

Research shows that endocrine related conditions impact the outcomes of patients with COVID-19.² There is recent evidence that people suffering from hormone conditions, such as diabetes and obesity, have more severe symptoms and health outcomes including death.^{31,32}

Complex socioeconomic factors also play a role in increasing the risk for diabetes, as well as for the epidemic of obesity coexisting with the COVID-19 pandemic. Further research is needed to understand the complex interplay of gender, ethnicity and economic status on increasing the susceptibility of people living with endocrine conditions to more severe illness. Vaccines are still recommended. A statement published in January 2021 from endocrine experts stresses that the recommendation for COVID-19 vaccination in patients with stable endocrine disorders should not be different from the one for the general population.³³

Multi-disciplinary nature of preventing, managing and treating endocrine disorders

The field of endocrinology has been revolutionised by advances in molecular biology, clinical chemistry, imaging, information technology and therapies, and has significantly advanced the modern concept of life sciences and biomedicine. The **close connection between research and clinical output is central to the discipline of endocrinology** and has contributed to advancing the medical field. It may not be coincidental that, in the past, the **impact of endocrinology in medicine was recognised by several Nobel Prizes** having been awarded to scientists for discoveries related to hormones.³⁴ Endocrinologists apply their knowledge in the clinic as well as in the laboratory, and as a result science merges with patient needs.

For instance, by regulating food intake and energy expenditure, hormones and their analogues represent the cornerstone of the pharmacotherapy of obesity. This process is helped by the fact that endocrinology is often tertiary centre based, and engaged with multidisciplinary and pan-European research projects such as ERCUSYN,³⁵ ENS@T³⁶ and ENETS.³⁷ This results in tailored therapies addressing endocrine needs and maintaining individual quality of life.

Endocrinology plays an important role in a multidisciplinary approach to develop better tools to identify chemicals with endocrine disrupting abilities essential for action on the reduction and prevention of further production, distribution and human exposure to major EDCs, thereby preventing their potential adverse effects on brain development, impaired fertility and major diseases such as obesity and cancer. For instance, the collaboration between endocrinology and toxicology is important to improve methods to identify chemicals as EDCs. Moreover, other disciplines like developmental medicine, biology or human epidemiology are needed to identify links, associations and exposures to chemicals.

Notably, advances within the field of endocrinology are not only important for the prevention, treatment and management of endocrine diseases. Endocrinology often plays a **fundamental role in the diagnosis and monitoring of prevalent non-endocrine diseases** in which hormones are used as biomarkers of disease (e.g., nt-proBNP, a type of protein produced by the heart, in heart failure) and treatment of non-endocrine diseases (e.g., erythropoietin for renal and other causes of anaemia). Improved cancer treatment outcomes come with long-term management of the consequences of the disease and its treatment by endocrinologists.³⁸

Novel immunotherapies against many different cancers often display severe side effects related to endocrine organs such as pituitary and thyroid permanent dysfunction and fulminant diabetes (a subtype of type 1 diabetes), that without a strong multidisciplinary approach may lead to anti-cancer drug discontinuation.

The complexity of the endocrine system means that there is a need for **multi-disciplinary integration of endocrinology in clinical practice**. Endocrinologists combine their practice with acute internal medicine and so are frequently caring for the most severe patients. Case in point: **the COVID-19 pandemic has seen endocrinologists at the frontline treating patients with the most critical symptoms** but also disclosing the clinical relevance of emerging endocrine features of COVID-19 such as calcium, vitamin D and fractures. For example, the improved treatment of hyperglycaemia has demonstrated that patients under good glycaemic control have a substantial decrease in mortality. Moreover, the management of nutritional support is crucial for preventing undernutrition and sarcopenia in these patients. An increased level of funding for basic as well as clinical research within the field of endocrinology

is critical for the future goals to prevent a range of endocrine related chronic, non-communicable diseases, for example, type 1 diabetes and obesity, and improve treatment and management of the cases we fail to prevent. In all priority areas we advocate for rigorous sex-specific research, which is particularly important for endocrinology.³⁹

How endocrinologists see the future

The Mapping Endocrinology in Europe (MEnEU) survey conducted by ESE in 2018⁴⁰ showed that:

- Nearly 80% of respondents expect patient numbers to increase, and for their issues to become more complex;
- Diabetes, obesity, metabolism and thyroid disorders command the highest workload in the clinic;
- In rare endocrine disease, an emphasis on improving diagnosis, developing guidelines and equal access to care and treatment is needed.

Endocrinologists who took the survey highlighted some of the most important priorities as:

- Protecting and further developing endocrinology as an attractive discipline to cover the increasing demand for endocrine expertise;
- Providing uniform quality education in institutions and European accreditation standards;
- Ensuring equality of care; ensuring equal access to diagnosis and medical care;
- Ensuring that research funding budgets are sufficiently allocated to the disciplines that need them most.



Hormones in European Health Policies: four key policy areas

Disruption of the normal functioning of the endocrine system can be caused by inherited genetic conditions, but also through the direct impact of external factors such as lifestyle, aggressive forms of medical treatments, and the environment we live in. The following chapters – obesity, rare disease, cancer and Endocrine Disrupting Chemicals – set out some of the key priority areas linked to endocrinology that are having some of the biggest effects on societal health and healthcare spending today and that are most relevant to the ambitions of European policymakers. While these areas deserve priority attention in European health policies, ESE remains engaged in securing better European and national health policies for all endocrine disorders.

Obesity

Obesity and the complex hormonal relationship

Obesity is defined as having abnormal or excessive fat accumulation that presents a risk to health.⁴ The traditional view of fat tissue (known as adipose tissue) is that it is an inactive reserve for energy storage – but in fact **fat is an endocrine organ, producing over 600 different hormones**.⁵ Adipose tissue is integrally involved in coordinating a variety of biological processes including energy metabolism, neuroendocrine function, and immune function.⁶

Obesity, a condition that is characterised by a disturbance in normal metabolic homeostasis, should therefore be defined as an endocrine condition, and is a direct result of a chronic imbalance between energy intake and energy expenditure with the excess energy stored in adipose tissue.⁴¹ Once obesity is present, weight reduction is difficult to accomplish, partly due to disturbances of appetite regulating hormones. Often extra therapies are necessary in addition to a healthy lifestyle and addressing negative social factors (e.g. poverty, stress). Treatments such as surgical or pharmacological interventions and cognitive-behavioural therapy may be required. People affected by obesity face major discriminatory attitudes in relation to employment, education and healthcare, as well as psychiatric comorbidities,⁴² when in fact they are suffering from a disease and should be receiving medical care.

The simplest way to diagnose obesity is by measuring Body Mass Index (BMI), an index that is defined as a person's weight in kilograms divided by the square of their height in metres (kg/m^2). For adults, the World Health Organisation (WHO) defines obesity as a BMI greater than or equal to 30, and generally speaking the higher the BMI the more body fat.⁴³

Although BMI provides a useful population-based measurement, it should be considered alongside other factors such as genetic predisposition, lifestyle (such as stress and lack of sleep), medication and environmental considerations such as EDCs, which are all contributing to the rise in obesity.⁴² Other methods in addition to BMI, such as skinfold measurement, are used to determine excess fat accumulation.

The two-way relationship between obesity and hormones is complex. Having an endocrine condition can be an underlying risk factor for obesity, and increased body fat can lead to a number of hormonal changes, such as insulin resistance,⁴⁴ low vitamin D and low testosterone levels. Indeed, several other endocrine disorders, including insulinoma (tumour of the pancreas), Cushing's syndrome, hypothyroidism, polycystic ovarian syndrome and growth hormone deficiency are all associated with obesity.⁴⁵

One example from the more than 600 hormones produced by fat tissue is the hormone leptin which, when it works as intended, suppresses appetite. However, people with obesity often develop excess leptin, leading to leptin resistance in the body – the leptin simply does not work as it should anymore. Obesity can also result from missing leptin or missing function of the leptin receptor, underscoring that this

is not a simple issue but a complex endocrine problem requiring endocrine solutions.⁴⁶ Moreover, several lipophilic EDCs accumulate in the adipose tissue. Thus, the adipose tissue serves as a reservoir of EDCs that can be released into the system in response to hormonal stimulation.

A global epidemic with associated comorbidities

Obesity is fast becoming the most prevalent health issue globally, **with estimations that more than half of all European adults are living with overweight or obesity.**⁴⁷ It is estimated that the global prevalence of **obesity has increased almost threefold since 1975, affecting 650 million adults in 2016.**⁴⁸

Obesity increases the risk of comorbidities, and is responsible for about 80% of cases of type 2 diabetes, 35% of ischaemic heart disease and 55% of hypertensive disease among adults in Europe.⁵ Obesity is also a gateway disease for certain cancers, with nearly 40% of all cancers attributed to overweight and obesity.⁶

The economic and psychosocial costs of obesity are striking. Coupled with the economic costs of the associated comorbidities, the impact on countries' healthcare systems and workforces is vast. In **2014, healthcare costs in Europe associated with overweight and obesity were estimated at €120.6 billion, and this is projected to rise by 63% to €197 billion by 2025.**⁴⁹

Paediatric obesity

Levels of paediatric obesity are also rising across Europe and despite policy efforts aimed at obesity prevention, many countries in the European Region as designated by the World Health Organisation (WHO) are continuing to struggle with increasing rates of childhood obesity.⁵⁰ It is estimated that **severe obesity affects some 400,000 of the estimated 13.7 million children aged between six and nine across 21 European countries.**⁵¹

Even in childhood, obesity is associated with socioeconomic costs and increases in healthcare expenditures. The first six months of life are a critical window for adiposity programming. A high concentration of EDCs during this vulnerable period via breastfeeding and/or the water in formula feeding has great input on adiposity programming, via disruption of appetite regulating hormones and hormones involved in metabolism. Children who are obese are more likely to remain so into adulthood, and obesity is associated with adolescent cancer prevalence, impacting healthcare systems and expenditure throughout their lifetime.⁴³

The heterogeneous nature of obesity means that it requires specialist knowledge by endocrinologists, working within a multidisciplinary team, to determine the cause and recommended treatment. The rise of childhood obesity has gained much well-deserved

attention in recent years, but it will be important not to neglect the policies required to address adult obesity as well, such as reimbursement for lifestyle and treatment options, and to include both prevention and treatment options over the entire course of life.

Obesity and COVID-19

There is growing evidence that people living with hormone conditions such as diabetes, obesity, adrenal insufficiency and Cushing's syndrome face an increased risk of severe infection with COVID-19. **Studies show that 26% of COVID-19 patients with a symptomatic disease had obesity,** 15% had diabetes and more than 30% had already suffered from bone fractures. These individuals had worse outcomes and poorer survival rates compared to people not suffering from obesity, diabetes or bone fractures.^{9,52,53,54}

Policy efforts in relation to COVID-19 are currently focusing on crisis management, vaccine research and development, and potential treatments. It will be important not to neglect the underlying conditions and factors that make populations vulnerable and exacerbate the COVID-19 pandemic. Prevention and research around the connection of COVID-19 to underlying health conditions such as obesity are critical in order to increase resilience and avoid overburdening healthcare systems.

Experts are warning that vaccines may not work as effectively in people who are obese and are calling for more of this population to be included in COVID-19 vaccine trials. Other existing vaccines are known to be relatively less effective in people who are obese. Although the definitive reason for this is not known, it could be due to factors such as inflammation caused by obesity changing the behaviour of cells that fight infection, fat tissue making it harder to reach the muscle with the vaccine needle, or the body requiring a higher vaccine dose.⁵⁵

“Body fat is not just a passive tissue for storage and isolation. More than 600 hormones and other substances are produced in body fat, which is an active organ. Some of the substances which are produced in fat have pro- or anti-inflammatory and immune functions, others affect appetite and metabolism and yet others affect the body’s sensitivity to insulin. So, fat is a conductor giving and receiving instructions to and from the brain and other parts of the body through the release of hormones. When the amount of fat becomes too large imbalances of the fat hormones occur, and these contribute to a state of chronic inflammation, with many adverse consequences. It seems also an important factor in the current COVID-19 pandemic in which obesity is a clear risk factor for a more serious course of the disease.”



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Obesity must urgently be treated as a chronic relapsing endocrine disease

Acknowledging the growing proportion of people suffering from obesity in Europe, the EU has created various initiatives and campaigns in recent years to help fight the disease. How obesity is regulated and prevented, and whether or not it is treated a disease, varies among European countries.

On the occasion of World Obesity Day 2021, the European Commission published a new dedicated brief on primary prevention of obesity in which obesity was categorised as a major non-communicable disease.⁵⁶ However, the European Commission has not yet taken measures to have obesity uniformly treated as a chronic endocrine disorder at European level, as recommended by many other members of the medical community.⁵⁷ Obesity is currently only classified as a disease in three European countries – Italy,⁵⁸ The Netherlands,⁵⁹ and Portugal.⁶⁰ Around the world, the United States, Canada and Israel also do recognise obesity as a disease. **Given the scientific evidence that it is an endocrine disease requiring endocrine solutions, ESE believes that all European countries should urgently and without delay classify obesity as a disease.** As an extension of this, the EU and governments across Europe should recognise the central role of hormones in preventing, treating and living with overweight and obesity.

The European Commission has drafted a number of initiatives and guidelines to support EU Member States, guided since 2007 by the Strategy on nutrition, overweight and obesity-related health issues.⁶¹ The strategy focuses on action that can be taken at local, regional, national and European levels to reduce the risks associated with poor nutrition and limited physical exercise, while addressing the issue of inequalities across Member States. Science has evolved rapidly over the past 14 years, and it is therefore high time to update this strategy to complement scientific advances and, importantly respond to the prevalence of obesity in Europe which has increased during this time.

Relevant regulation also exists in other interlinked areas where the EU does have legislative powers, such as the Food Labelling Regulation,⁶² which makes it mandatory to provide nutritional information. The Farm to Fork Strategy, a key element of the 2019–2024 Commission’s Green Deal, promises to take this further, through focusing on ensuring food security, nutrition and public health. In fact, one of the targets of the Strategy is to reduce obesity by introducing healthy lifestyle habits among the population and trying to promote better nutrition. However, there is still room to reinforce both the ‘farm’ and the ‘fork’ side of the Farm to Fork Strategy to phase out endocrine disrupting crop protection products and use the momentum to encourage healthy lifestyle habits as well as environments and price incentives that stimulate healthy behavior with respect to nutrition and exercise. Encouragingly, the Horizon Europe Work Programme for 2021–2022 will allocate part of its funding to obesity.

Within the research funding provided to address the consequences of COVID-19, obesity has not yet been given sufficient attention.⁶³ Partnering with scientific societies such as ESE and EASO, and multi-stakeholder initiatives such as OPEN-EU, would help policymakers find efficient and comprehensive solutions for emerging issues, from the obesity epidemic itself to how it overlays with the global COVID-19 pandemic.

Rare endocrine diseases

Rare endocrine disease in Europe

Rare diseases, which affect fewer than 1 in 2,000 people,¹³ are less well known and researched than more prevalent diseases, but cover a wide range of conditions. **Despite their rarity, these conditions collectively affect approximately 30 million people across Europe**¹³ and come with particular challenges related to time to diagnosis, the need for innovative treatment options, and investment into research. Due to the limited amount of strong epidemiological data, the real prevalence and incidence of many of these rare diseases is not known.

Rare endocrine diseases include inherited disorders (e.g., congenital adrenal hyperplasia), cancer (e.g., multiple endocrine neoplasia syndromes), and conditions associated with metabolic disorders such as diabetes, calcium and bone metabolism, lipid metabolism, hypogonadism, and adrenal, pituitary and thyroid dysfunction.⁶⁴ For paediatric and adult endocrinologists care for patients with rare diseases constitutes a key focus for their activities, due to the multitude of diseases with an endocrine component or origin.

According to the European Registries for Rare Endocrine Conditions⁶⁵ there are over 440 distinct rare diseases that affect the endocrine system.⁶⁶

It is estimated that it takes an average of four years to receive a rare disease diagnosis.⁶⁷ Rare endocrine diseases are often chronic and life-threatening⁶⁸ and accurate estimations of their genuine economic cost and societal burden have not been properly quantified in the EU. Many rare diseases involve paediatric populations, which brings severe societal and healthcare costs, and limited future opportunities in life for the individuals affected by these diseases and their families.

Advances in the management and treatment for rare endocrine conditions are being made, including for pituitary disease, hypoparathyroidism, some rare bone and lipid disorders, and rare diseases affecting children.¹⁴ However, new strategies to fund research and clinical trials for conditions that affect a small number of patients – and therefore do not represent attractive commercial value for innovative medicines – need to be developed.

European Reference Networks (ERNs)

ERNs have been instrumental in creating clearly defined structures for sharing knowledge and care coordination for specific rare diseases across the EU.⁶⁹ Certain ERNs incorporate rare endocrine diseases into their health remit including Endo-ERN,⁷⁰ BOND-ERN,⁷¹ MetabERN,⁷² and EURACAN.⁷³



Name of network	Geographical reach	Thematic groups
<u>Endo-ERN</u> The European Reference Network on Rare Endocrine Conditions	71 reference centres & 15 affiliated partners in 27 countries	• Adrenal disorders • Disorders of calcium and phosphate homeostasis • Disorders of sex development and maturation • Genetic disorders of glucose and insulin homeostasis • Genetic endocrine tumour syndromes • Disorders of growth and genetic obesity syndromes • Pituitary disorders • Thyroid disorders
<u>ERN-BOND</u> The European Reference Network on Rare Bone Diseases	17 expert centres from 10 EU Member States	• Osteogenesis imperfecta • Achondroplasia • Hypophosphatasia • Multiple osteochondromas • Fibrous dysplasia / McCune-Albright syndrome • Pseudopseudohypoparathyroidism • Other rare bone diseases (hypophosphataemia, fibrodysplasia ossificans progressiva, others)
<u>MetabERN</u> The European Reference Network for Hereditary Metabolic Diseases	78 healthcare providers in 23 EU Member States	• Amino acid and organic acid diseases • Disorders of pyruvate metabolism, mitochondrial oxidative disorders, thiamine transport and metabolism • Carbohydrate, fatty acid oxidation and ketone bodies diseases • Lysosomal storage diseases • Peroxisomal diseases and lipid related disorders • Congenital disorders of glycosylation • Neurotransmitter and small molecule disorders
<u>EURACAN</u> The European Reference Network for Rare Adult Solid Cancers	66 healthcare providers in 17 European countries, and 22 Associate Partners including European Patient Advocacy Groups and rare disease stakeholders	• Sarcoma of the soft tissue, bone and viscerae (Sarcoma) • Rare neoplasm of the female genital organs and placentas • Rare neoplasm of the male genital organs, and of the urinary tract • Neuroendocrine tumours • Rare neoplasm of the digestive tract • Rare neoplasm of endocrine organs • Rare neoplasm of the head and neck • Rare neoplasm of the thorax • Rare neoplasm of the skin and eye melanoma • Rare neoplasm of the brain and spinal cord

Table 1 – Examples of ERNs and their activities. This table was developed in November 2020

These knowledge-based networks have been critical in shaping the rare disease policy space. However, **greater support from the EU is needed to improve their functionality and to improve health outcomes in rare disease patient populations.**

Although Europe is ahead of other regions with regard to reference networks, the level of funding is not sufficient to allow for lead research projects to be undertaken within these networks. Funding and resources to manage projects and ERN infrastructure and to be able to collect good quality data in these registries is required,

as currently endocrinologists focused in this area have limited capacity to be involved with these programmes.

Experts advise that many countries in Europe are not aware of the existence of these reference networks, so increased promotion within the medical community and towards European and national institutions is needed. Moreover, interaction between European and national institutions should also be fostered.

The EU should continue evolving and expanding funding for ERNs so that they can expand their activities, for example through the research programme Horizon

Europe, which should play a more prominent role in supporting the ERNs due to their significance for European research in the area of rare cancers and other rare diseases. Increased funding would also help the ERNs better coordinate the projects and their infrastructure and compensate patients and the medical/academic communities for giving their valuable time to the study of these diseases.

“As a patient, I really appreciate the founding of ERNs because for the first time, patients are really part of a network in which they have the opportunity to work side by side with healthcare professionals and give their opinion on important matters concerning them. For example, endocrine patients all over Europe were recently asked for their opinion on patient information materials and their unmet needs in medical research. The outcomes of these surveys will be used to shape the research agenda and will give insight into how to reach out to even more patients in the future. Patient representatives are involved on a voluntary basis and though Endo-ERN does its utmost to make their involvement possible, improved funding mechanisms would enable the ERNs to compensate patients better for their time.”



Johan de Graaf,
Dutch Pituitary Foundation
ERN patient representative,
living with pituitary adenoma/
hypopituitarism

Rare endocrine diseases and COVID-19

People living with certain rare diseases may have a higher risk of serious illness from COVID-19.⁷⁴ There is uncertainty around the risks of serious disease in this community due to the difficulties in prognosis and the small number of people affected, who can often have very individualised symptoms and comorbidities.⁷⁵ Further research in this area and support for some of the most vulnerable patients, whose feelings of isolation may be exacerbated at this time, is needed. **According to a study by EURORDIS, COVID-19 caused severe disruptions to care for 83% of people living with a rare disease.**⁷⁶

The ESE Rare Disease Committee, alongside ENDO-ERN, has engaged in an initiative to collect essential data concerning specific groups of patients with rare endocrine conditions, who are also affected by COVID-19. This project is designed to understand the occurrence of a wide range of conditions to allow the clinical networks to objectively map the conditions and activity.⁷⁷ Similar initiatives should be stimulated across

the EU to obtain a better understanding of the links between rare (endocrine) diseases and COVID-19. On a more positive note, COVID-19 has fostered the uptake of digital tools for patients, including for example virtual consultations. These digital tools may help improve care and patient outcomes in the future.

A unique European opportunity to improve livelihoods for rare disease patients

In addition to the ERNs, the EU institutions have developed a number of programmes focused on financing research and innovation in the area of rare diseases. The main tool through which the European Commission has been contributing to this is the EU Framework Programmes for Research and Innovation. Altogether more than €1 billion has been committed in collaborative research through the Seventh Framework Programme (FP7)⁷⁸ and Horizon 2020⁷⁹ in more than 200 projects related to rare diseases. Many of these projects link with the ERNs.

The EU4HealthProgram,⁸⁰ drafted by the European Commission in the wake of COVID-19, makes reference to the specific burden of rare diseases on the challenges faced in the areas of health security and health systems. Concretely, the EU4Health package promises a welcome scale-up of networking and extending the ERNs to non-communicable diseases. Furthermore, the EU also pursues efforts to increase visibility in the public domain on the topic of rare diseases and supports the national plans for rare diseases in EU countries. The EU should ensure comprehensive implementation of National Rare Disease plans, as these plans help give rare diseases high relevance among national health policies.

There is an established legislative framework to provide incentives for the development of drugs for rare diseases (orphan medicines). The Regulation on Orphan Medicinal Products⁸¹ was first adopted in 2000 to encourage pharmaceutical companies to develop medicines for rare diseases. A number of drugs in the pituitary, bone and calcium, and rare lipid disease areas have benefitted from coming to market with the orphan designation. An evaluation of this legislation was published in August 2020⁸² – the next expected step is an Impact Assessment of possible legislative options. This evaluation is an opportunity to support an effective instrument for channelling R&D into specific therapeutic areas and the development of pathways in national pricing and reimbursement schemes to better assess the value of these type of medicines. Regardless of how the impact assessment progresses, rare disease patients would benefit if governments increase funding for Orphan Medicinal Products to provide better incentives for the development of medicines.

Furthermore, one of the main problems faced by medicines for rare diseases is reimbursement. The bar for orphan medicines is very high; health technology assessment bodies and payers expect the same

robustness of evidence as compared to medicines for other more prevalent diseases. However, the scientific evidence is more difficult to gather due to the rarity of the diseases they are meant to treat.

European Health Technology Assessment (HTA) legislation is therefore another avenue that could improve accessibility for patients with rare diseases. The HTA file has been underway for several years now, but it had not progressed since Council discussions in 2019.⁸³ In April 2021, the Council agreed on its negotiating mandate which will hopefully unlock negotiations with the European Parliament. The legislation aims

to provide EU-wide assessment of how new health technologies compare with existing treatments. The EU should urgently move forward on European-level HTA legislation and joint funding to make medicines for rare diseases available and affordable in all EU countries. Some progress has been made in the framework of the European Network for Health Technology Assessment (EUnetHTA) which aims at defining and implementing a sustainable model for the scientific and technical cooperation on HTA in Europe. Nevertheless, this effort is voluntary for Member States and its impact is yet to be seen.⁸⁴

Cancer and endocrinology

Cancer is the second leading cause of death and morbidity in Europe, with more than 3.7 million new cases and 1.9 million deaths each year.¹⁶ It is estimated that 40% of all EU28 citizens will face cancer at some point in their lives.⁸⁵ Cancer care is rapidly evolving, with the costs of treatment frequently debated. Studies in 2018 show that in Europe, the estimated costs of cancer to society were approximately, in the region of €199 billion.⁸⁶

The interaction between endocrinology and cancer is complex, and new research has highlighted the intricate nature of this interaction in terms of prevention, treatment and post-treatment care.

There are five significant ways in which the endocrine system relates to cancer:

- 1. Classic endocrine cancers.** Certain endocrine cancers are on the rise. Thyroid cancer has seen increases of >50,000 new cases per year,⁸⁷ and more than 60% of neuroendocrine tumours (NETs) are diagnosed at a late stage, impacting the outcomes of these cancers.⁸⁸ The incidence of breast and testicular cancers is also on the rise.^{89, 90}
- 2. Hormone-dependent cancers and their endocrine treatments.** For instance, prostate cancer or breast cancer antiandrogens/antiestrogens have endocrine side effects (muscle and bone loss, fractures, cardiometabolic risk).
- 3. Long-term effects of cancer treatments.** The endocrine system is vulnerable to aggressive anti-cancer treatments that result in endocrine comorbidities in cancer survivors.⁹¹
- 4. Obesity as a risk factor.** Obesity has been identified as an independent risk factor for many cancers, with nearly 40% of all cancers attributed to being overweight and obese.⁷ In particular endometrial,

postmenopausal breast and colorectal cancer – all related to the endocrine system – account for many of the cancers attributed to obesity.

- 5. The impact of environmental factors.** Exposure to EDCs is known to have an effect on different hormones, and is associated with reduced fertility, impaired neurodevelopment, and the development of obesity and cancer.^{92,93,94,95}

Endocrine cancers

Endocrine cancers begin in the glands that secrete hormones. Tumours can occur in any of the major glands of the body, including the thyroid, pituitary and adrenal glands, and the pancreas.⁹⁶ In addition, because endocrine tumour cells grow from cells that produce hormones, the tumour itself can produce hormones that can cause serious illness.⁹⁷ As an example, endocrine glands such as the testis or the ovary can be affected by malignancies and have negative impacts on basic functions like reproduction.

Endocrine cancers are considered rare, but despite this, certain types are on the rise. **The most common type of endocrine cancer is thyroid**, which has seen increases of more than 50,000 new cases per year⁸³, **and is now the second most common cancer in young women after breast cancer**.⁹⁸ Although some of the increase in incidence is likely to be due to improved detection at the early stages of the disease, other factors such as obesity have been identified as contributing to the increase in incidence rates.^{99,100} Another example is neuroendocrine tumours (NETs). NETs originate from neuroendocrine cells that are the intersection between the nervous and endocrine systems. Neuroendocrine cells are found in organs throughout the body (pancreas, lung and breast, to name a few), and perform specific functions such as regulating the air and blood flow in the lungs and the speed at which food moves through the gut.⁹³ Although NETs are also considered as rare, their incidence and prevalence has been steadily rising.¹⁰¹ As they are frequently diagnosed late due to their body-wide presentation and variability, patients generally experience worse outcomes, with the median survival for patients with advanced NETs at just 33 months.⁸⁴

Endocrine cancers can also be very aggressive. For instance, adrenocortical carcinoma (ACC) is one of the most aggressive endocrine cancers originating in the cortex layer of the adrenal gland.¹⁰² ACC is a rare malignancy, affecting 1.5–2 persons per million each year. It is slightly more common in women and has a higher incidence in children younger than five years and middle-age adults. Patients may present with an asymptomatic tumour incidentally found, or with a variety of symptoms induced by hormonal hypersecretion from the tumour and producing a characteristic clinical syndrome including Cushing's syndrome, Conn syndrome, virilisation and feminisation. Moreover, ACC has often invaded nearby tissues or metastasised to distant organs at the time of diagnosis. As with other endocrine cancers, despite improved methods of diagnosis, ACC usually presents at an advanced stage and as a result five-year survival ranges from 20% to 45%.¹⁰³

"I was diagnosed with a NET 14 years ago. By then I had already had it for 5 years. That is not uncommon – the known average for correct diagnosis of a NET is 5-8 years. Most of us are diagnosed after the cancer has already metastasised. You can live with a NET, but it is expensive as it requires constant treatment with rare medicines. Living with a NET often comes with side effects and a very specific diet, yet there are not many nutritionists who understand this condition. Quality of life and mental health (also for the partners) of people living with a NET is a real struggle. It can be cured only if it is found very early, which is why investment in early diagnosis, including through the education of gastroenterologists, is so important."



Michael Rosenberg,
Founder of the Middle East
Neuroendocrine Tumour Society
(MENETS), living with a pancreatic
neuroendocrine tumour

The effects of aggressive cancer treatments on the endocrine system

The endocrine system is particularly sensitive, meaning that aggressive anti-cancer treatments can have a significant effect and result in hormone-related comorbidities. These can include:

- Functional alterations in hypothalamic-pituitary, thyroid, parathyroid, adrenal and gonadal regulation¹⁰⁴;
- A high risk of irreversible infertility in young individuals, especially boys, treated with chemotherapy⁹⁷;
- Bone, obesity and metabolic complications¹⁰⁰;
- Autoimmune endocrine dysfunctions associated with cancer antibody immunotherapies, where the treatments cause a raised immune response leading to immune-related adverse events¹⁰⁵;
- An increased risk of subsequent malignancies to the endocrine organs (e.g., thyroid) caused by radiotherapy.¹⁰⁰

As new advances in cancer treatments continue to be developed, it will be important to consider the long-term impact on the body's endocrine system, and the importance of the multi-disciplinary team in charge of patient care. Quality of life for cancer survivors also deserves increased attention – before, during and for the years after they undergo treatment. Their mental health, their relationships, their careers and their diets are often turned upside down when the cancer diagnosis is received.

Endocrine cancer and obesity

Obesity is a major risk factor for developing cancer.¹⁰⁶ The International Agency for Research into Cancer and the World Cancer Research Fund (WCRF) report that there is strong evidence to show that obesity is associated with endometrial, oesophageal adenocarcinoma, colorectal, postmenopausal breast, prostate and renal cancers.¹⁰²

Understanding the mechanisms of how cancer and obesity are linked will help in developing innovative strategies for prevention and treatment in these types of cancer.

A recent study of 2.3 million adolescents showed that adolescent obesity is linked to cancer risk in midlife,¹⁰⁷ and there is a clear trend that obesity-related cancers are diagnosed increasingly at younger ages.¹⁰⁸ It is important to improve early detection and diagnosis of endocrine cancers, often presenting in children and young adults.

In this regard, Multi-Disciplinary Teams (MDTs) are of great importance. A multidisciplinary approach offers the best prospect for improving clinical outcomes and understanding the natural history of neuroendocrine neoplasms (NENs), for example. NEN patient management is often complex and challenging, and may require a combination of surgery, systemic treatments and locoregional approaches, on top of a specialised platform including nutritional, palliative, social and psychological support. Endocrine tumours in general, including those of the pituitary gland, are always cared for by MDTs.

The Beating Cancer Plan and the European research agenda need a strong endocrinology focus

Cancer is recognised as a major health issue and therefore the EU treaties give the EU competence to support, coordinate or supplement the actions of Member States. The EU has adopted a plethora of initiatives, including a Council Recommendation on Cancer Screening in the EU,¹⁰⁹ Council conclusions on reducing the burden of cancer,¹¹⁰ a European Code Against Cancer¹¹¹ and European guidelines for quality assurance in breast, colorectal and cervical cancer screening.¹¹² While these show good progress, no initiative has yet sufficiently addressed the complex relationships between cancer and the endocrine system.

Cancer is one of the main priorities of European Commission President Ursula von der Leyen and Health and Food Safety Commissioner Stella Kyriakides. **The cornerstone of this commitment is the European**

Beating Cancer Plan which is based on four main pillars: prevention, early diagnosis, treatment and follow-up care. **The European Union should include the endocrinology perspective (and acknowledge endocrine cancers) in the implementation of this plan and other cancer-related policies.** This means making prevention a focus area and ensuring that ERNs have a key role in improving early detection, diagnosis and treatment. Future policies should also ensure that other medical disciplines are trained in endocrine cancers – for example that gastroenterologists are trained to recognise NETs.

In addition, national cancer action plans should address comorbidities in cancer survivors and the EU should promote an ongoing and multidisciplinary approach to prevent and mitigate cancer interventions resulting in hormone related comorbidities due to the sensitivity of the endocrine system.

In terms of research funding, the EU should through the Horizon Europe Mission Board for Cancer and other mechanisms direct future cancer funding towards academic consortia to study evolving epidemiological trends of (endocrine) cancers and improve current diagnostic processes, for example by improving the current late diagnosis of NETs.

Endocrine Disrupting Chemicals (EDCs)

EDC exposure and health risks

Endocrine Disrupting Chemicals (EDCs) are substances that mimic, block, or interfere with hormones in the body's endocrine system. Recent studies estimate that EDCs contribute substantially to disease and disability across a person's lifetime, costing hundreds of billions of euros per year.²⁰

EDCs are found in everyday consumer items including detergents, flame retardants, food additives, children's toys, sunscreen, textiles, anti-bacterial soaps, cosmetics, plastic bottles, metal food cans and pesticides.

Category/Use	Example EDCs
Pesticides	DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate
Children's products	Lead, phthalates, cadmium
Food contact materials	BPA, phthalates, phenol
Electronics and building materials	Brominated flame retardants, PCBs
Personal care products, medical tubing	Phthalates
Antibacterials	Triclosan
Textiles, clothing	Perfluorochemicals

Table 2: Some known EDCs and their uses

Source: Crews, David. (2015). Introduction to EDCs: A guide for public interest organizations and policymakers. Strategic Approach to International Chemicals Management (SAICM), IPEN, and The Endocrine Society

Abbreviations: BPA: bisphenol A; 2,4-D: 2, 4-dichlorophenoxyacetic acid; DDT: dichlorodiphenyltrichloroethane; PCBs: polychlorinated biphenyls

Exposure to EDCs happens on a daily basis through consumption of food and water, through the skin (via e.g., cosmetics), by inhalation and by transfer from mother to foetus (across the placenta) or mother to infant (via lactation).¹¹³

Some EDCs are slow to break down and persistent in the environment, making them potentially hazardous over time, and even low doses of EDCs can affect hormone levels.¹¹⁴ EDCs can also enter the environment through industrial and urban discharges, agricultural run-off and the burning and release of waste.¹¹⁵

Health risks associated with EDCs

There are multiple adverse health outcomes associated or linked with exposure to EDCs, suspected to lead to diseases such as altered reproductive function in men and women, abnormalities in sex organs, endometriosis, early puberty, altered nervous system development and function, immune function disorders, cancers, neuroendocrine tumours, respiratory problems,

diabetes, obesity, cardiovascular conditions, neurological issues and learning disabilities.¹¹

An especially challenging aspect of EDCs is their negative impact upon foetal development. EDC exposure in pregnancy is associated with variations in the gestational endocrine environment, including altered levels of sex steroids. Evidence indicates that EDCs, such as Bisphenol A, have been linked to adverse pregnancy outcomes including miscarriage, preterm labour, preeclampsia and foetal growth restriction.^{116,113} During foetal maturation, EDCs can compromise normal developmental processes which can predispose foetuses to adverse health risks later in life.¹¹⁷ Furthermore, the impact of EDCs can be transgenerational and the detrimental effects may be lifelong.¹¹⁸ The adverse health impact of EDCs continues into infancy and childhood and they are characterised by disruption of the regulation of hormones, immune system, adiposity programming, neurocognitive development and other functions. As mentioned in the obesity chapter, a high concentration of EDCs during the first six months of life via breastfeeding and/or the water in formula feeding has great input on adiposity programming and therefore future obesity risk, via disruption of appetite regulating hormones and hormones involved in metabolism.

The link between EDCs and cancer, including breast¹¹⁹ and testicular cancer,^{88,90} is the subject of many studies. Per- and polyfluoroalkyl substances (PFASs), widely used for their desirable properties (e.g., being stable under intense heat), have been associated with the early onset of menopause in women.¹²⁰

Despite their known impact on health, EDCs are still widely produced, distributed and prevalent in Europe and disproportionately affect vulnerable populations. The COVID-19 pandemic has demonstrated that achieving a non-toxic environment is more urgent now than ever before, particularly in the prevention of diseases such as diabetes and obesity, conditions that result in greater morbidity and mortality, as well as greater requirements for ICU and significant medical support.¹²¹

The economic costs of EDCs

Economic analysis reveals that EDCs cost the EU28 between €157 and €270 billion per year in healthcare expenses and lost earning potential, which equates to up to 2% of European GDP.¹²² Large contributors to these figures were shown to be neurodevelopmental and metabolic disorders as well as cancer. EDC-driven obesity and diabetes alone cost between €18–€29 billion per year in the EU28.¹²³

Endocrinologists have an important role in the core research around the impact of EDCs, especially in newborns and children, as well as the treatments and care that are needed to support these patients.

“The current policy and legislative framework at the EU level related to EDCs is inconsistent and incomplete. The scientific endocrine community must work closely with other relevant scientific disciplines and decision makers to ensure future policies and legislation are consistent and better correlate with the latest scientific developments in the EDC field. The 2020 Chemicals Strategy for Sustainability is a good step in the right direction and we eagerly await its full implementation.”



Professor Josef Köhrle,
Institute of Experimental
Endocrinology, Charité –
Universitätsmedizin Berlin and Chair
of the ESE EDC Working Group

Now is the time to apply the precautionary principle and phase out EDCs

The EU has the obligation and urgent need to apply the precautionary principle to EDCs, to avoid the further production, distribution and exposure to pesticides, biocides or consumer products containing suspected EDCs. While the EU does not have a high degree of legislative power for most healthcare files, the EU institutions have strong competences to regulate the use of chemicals. The EU has already applied this competence to introduce specific legislative obligations aimed at phasing out EDCs in several legislations, including the umbrella REACH Regulation,¹²⁴ the 2017 Medical Devices Regulation,¹²⁵ and most recently and specifically through designating EDC criteria under the Plant Protection Products Regulation¹²⁶ and the Biocidal Products Delegated Regulation¹²⁷ in 2018 and 2017, respectively.

However, definitions, criteria for identification data and testing requirements for EDCs widely diverge in EU legislation, which has led to numerous legislative loopholes. For example, the criteria under the Plant Protection Products and the Biocidal Products Regulations do not yet serve to fully capture all substances that could cause potential harm and do not align in their data requirements to identify a substance as being an EDC. They are only ‘very similar’, which already creates a fundamental issue provoking confusion, conflicts and lack of practicability and credibility. This is strengthened by the fact that the information requirements within the two regulatory frameworks diverge, leading to different levels of confidence in the identification. And although the European Commission has acknowledged the existence of the ‘cocktail effect’, aggregated exposure of humans and wildlife to one or different EDCs in its

Communication “towards a comprehensive European Union framework on endocrine disruptors”,¹²⁸ current policies do not address this aspect.

As a first step towards addressing these issues, the Commission in 2020 carried out a Fitness Check¹²⁹ of the management of EDCs in a broad range of legislations.¹³⁰ The result of a public consultation¹³¹ on this was presented at the 2nd annual EDC forum in December 2020.

Addressing EDCs is a priority within the Green Deal, and the Chemical Strategy for Sustainability presented in October 2020 is a promising step. The call for a toxic-free environment and the commitments to investing in science and in chemicals that are safe and sustainable by design are other important steps. Importantly, the European institutions should implement without delay the proposal for legally binding hazard identification of EDCs, the inclusion of EDCs as a category of substances of very high concern (SVHCs), the phase-out of EDCs in consumer products, and the implementation of risk assessment factors for mixtures.

The Farm to Fork strategy, another element of the Green Deal, foresees a welcome reduction in agricultural chemicals and hazardous pesticides by 50%, which – together with the inclusion of EDCs as SVHCs foreseen under the Chemical Strategy for Sustainability – would serve to reduce the European population’s exposure to EDCs.

It also is of utmost importance that the policy actions following the Beating Cancer Plan recognise the role of EDCs in cancer and consider the necessary steps to reduce human exposure.



Conclusions and policy recommendations

Hormones determine growth, how our metabolic system works, our cognitive processes and our overall well-being every day. A lack of hormonal balance is linked to a wide range of health issues with enormous socioeconomic impact including obesity, cancer, diabetes, infertility, osteoporosis and a range of rare diseases. The interplay with these issues and COVID-19 cannot be overstated and is an important piece in the puzzle as we battle this global pandemic.

The European Union and national governments across the European region can all make a significant difference in addressing the many challenges in the field of endocrinology and the increasing importance of the endocrine specialty. Taking action now will not only save time and funds, but also save numerous lives in the years to come.

Throughout this paper we have explained the links with these issues focusing on four key topics which are closely related: obesity, rare diseases, cancer and EDCs. We have also examined the links between these four topics, hormones and COVID-19.

To properly address existing issues and achieve better hormonal health in Europe, the European Society of Endocrinology and our affiliated societies recommend the following:

Obesity

- **Recognise the central role of hormones** in preventing, treating and living with overweight and obesity;
- **Treat obesity as a disease** at the EU level and in all countries in the European region;
- Reinforce the 'fork' side of the Farm to Fork Strategy and encourage healthy lifestyle habits;
- Reinforce the 'farm' side of the Farm to Fork strategy by phasing out crop protection products containing EDCs;
- Update the 2007 Strategy on nutrition, overweight and obesity-related health issues;
- Put appropriate resources behind prevention, treatment and living with obesity;
- Develop comprehensive prevention policies including public awareness campaigns and national action plans;
- **Partner with scientific societies such as ESE and EASO** and multi-stakeholder initiatives such as OPEN-EU to find efficient and comprehensive solutions.

Rare endocrine disease

- As indicated in the EU4Health Package, **continue to evolve and increase funding for ERNs so that they can expand their activities**, including through Horizon Europe, which should play a more prominent role in supporting the ERNs due to their significance for European research to:
 - Extend the coordination of projects and their infrastructure;
 - Compensate patients and the medical/academic communities for giving their valuable time to the study of these diseases;
 - Create a pan-EU data acquisition strategy to improve current rare disease registries in a common and uniform data space, for instance through the European Health Data Space.
- **Increase funding for Orphan Medicinal Products** to provide better incentives for the development of medicines for patients with rare (endocrine) diseases.
- **Reform funding structures** (or value assessment principles) to provide incentives to invest in the use of 'old' medicines for new purposes;
- **Move forward on European-level Health Technology Assessment (HTA)** legislation and joint funding to make medicines for rare diseases available in all EU countries;
- Make the European research and reference networks inclusive and available also to countries neighbouring the EU;
- The EU should ensure comprehensive implementation of National Rare Disease plans, as these help to give rare diseases high relevance among national health policies.

Cancer

- **Strengthen the endocrinology perspective (and acknowledge endocrine cancers) in the implementation of the Beating Cancer Plan and other cancer-related policies, including through:**
 - Ensuring more prevention measures related to EDCs and obesity;
 - Ensuring that ERNs have a key role in improving early detection, diagnosis and treatment;
 - Encouraging National Action Plans to address comorbidities in cancer survivors;
 - Considering a pan-European and comprehensive approach to cancer, including the creation of pan-European databases for major and rarer endocrine-related cancers.
- **Promote an ongoing and multidisciplinary approach towards cancer survivors** to prevent and mitigate cancer interventions resulting in hormone-related comorbidity;
- Through the Horizon Europe Mission Board for Cancer and other mechanisms direct future cancer funding towards academic consortia to study evolving epidemiological trends of (endocrine) cancers and improve current diagnostic processes (for example improving the current late diagnosis of neuroendocrine tumours);
- **Promote further investment in diagnosis**, and in particular education and training of physicians so they are able to recognise potential endocrine cancer threats better;
- **Pay further attention to rare (endocrine) cancers** and make full use of the opportunities for cross-border support, guidance and innovation.

Endocrine Disrupting Chemicals

- **Strictly follow the precautionary principle**, to avoid production, distribution and exposure to pesticides, biocides or consumer products containing suspected EDCs;
- **Implement without delay the many actionable proposals in the Chemicals Strategy for Sustainability** and:
 - Establish a legally binding hazard identification of EDCs, binding criteria for EDCs under REACH and improve the existing criteria for plant protection products and biocides to lower the burden of proof and restrict more harmful substances;
 - Introduce criteria for chemicals that are safe and sustainable by design;
 - Develop a generic approach to assessing chemicals and registering polymers of concern;
 - Include EDCs as a category of Substances of Very High Concern (SVHCs) under REACH;
 - Close all legislative loopholes to prevent the possibility under EU law to 'rehabilitate' a compound identified as an EDC under other EU legislation;
 - Address EDCs and mixture effects as foreseen through the Chemicals Strategy for Sustainability and following the acknowledgement of these effects by the European Commission in its 2018 Communication on Endocrine Disruptors;¹³²
 - Raise awareness about EDCs and create an EU portal to inform citizens about the hazard and risks of exposure to EDCs;
 - Promote further EDC research and innovation to find safer alternatives for known and suspected EDCs.



About European Endocrinology and the European Society of Endocrinology

Endocrinology is a multidisciplinary, cross-cutting discipline. Endocrinologists touch upon many disease areas. Similarly, many other disease area experts are involved in the endocrinology discipline. Endocrinologists are based in hospitals, universities, specialised clinics and expertise centres across Europe and the world.

ESE and European Endocrinology

At the [European Society of Endocrinology \(ESE\)](#), we are working together to develop and share the best knowledge in endocrine science and medicine. Through our association with National Endocrine Societies, ESE represents a community of over 20,000 European endocrinologists, enabling us to inform policymakers on health decisions at the highest level through engagement in advocacy efforts across Europe. It is by uniting and representing every part of the endocrine community that we are placed in the best possible position to improve life for the patient.

The ESE Foundation – bringing ESE closer to the heart of Europe

In 2020, ESE founded the Hormone and Metabolism Foundation ('The ESE Foundation').

The overarching aim of the ESE Foundation is to benefit the broader public, with the endocrine patient at its core. The Foundation's aims are to promote endocrine health, address endocrine disease and improve patient care.

The ESE Foundation will promote ESE's work in areas such as:

- Raising funding and distributing funds with a particular focus on improving research and clinical outcomes for patients across all endocrine disciplines;
- Interacting with the European Union institutions to support the policy and advocacy needs of the endocrine community across Europe and to further ESE's policy and advocacy strategy;
- Raising the profile of endocrinology on a European and international basis with a focus on public engagement.

The ESE Foundation is a separate legal entity to the European Society of Endocrinology (ESE) and is registered in Brussels as a private foundation. The ESE Foundation is located at Avenue des Arts 56, 1000 Brussels, Belgium.

More information can be found at [https://www.e-se-hormones.org/about-us/e-se-foundation/](https://www.ese-hormones.org/about-us/e-se-foundation/)

European endocrinology is a collaborative effort

Together with other societies in the field of endocrinology, ESE aims to raise the profile of European endocrinology through greater collaboration between the different endocrine societies of Europe.

This network of societies can be a major contributor to the policy debate – as in this paper – to determine what is important to endocrine health and disease, to inform the debate between European and national levels and to help develop effective policies to improve health for European citizens. Through guideline development, educational activities, data dissemination and international collaboration ESE and its associated societies work together to raise the standards of care throughout Europe. As such, the different societies can support policymakers in securing that when policies are decided, these are implemented and their impact can be assessed.

In the area of Rare Endocrine Disorders, ESE supports and works together with Endo-ERN, the European Reference Network focused on endocrine disorders. A specific example of this collaboration is the ESE Rare Disease COVID-19 Task Force, aiming to map the impact of COVID-19 on patients with rare endocrine disorders.

ESE works closely with the ESE Young Endocrinologists and Scientists (EYES) network to ensure that their needs are being met. The EYES Committee communicates the opinions, suggestions and expectations of early career endocrinologists and scientists to ESE, and takes appropriate initiatives, supported by ESE.

ESE provides a support network and resources for endocrine nurses based in Europe. The ESE Nurse Committee is responsible for promoting education, training and mentorship for endocrine nurses across Europe. This committee also provides a support network for endocrine nurses, promotes advanced nursing practice and raises the profile of endocrine nursing within the multidisciplinary world of endocrinology.

ESE engages with Patient Advocacy Groups to advance patient education, provide groups the opportunities to interact with the clinical community, and discuss and address some of the barriers that may prevent patients in Europe from having equal access to the best diagnosis and care.

ESE is grateful for the efforts of its pharmaceutical industry partners to advance new diagnostic tools and develop therapeutic solutions, many of which are in the rare disease area, as well as to support the aims of the society and its members through support for research and education. A full list of the ESE Corporate Members can be found [here](#).

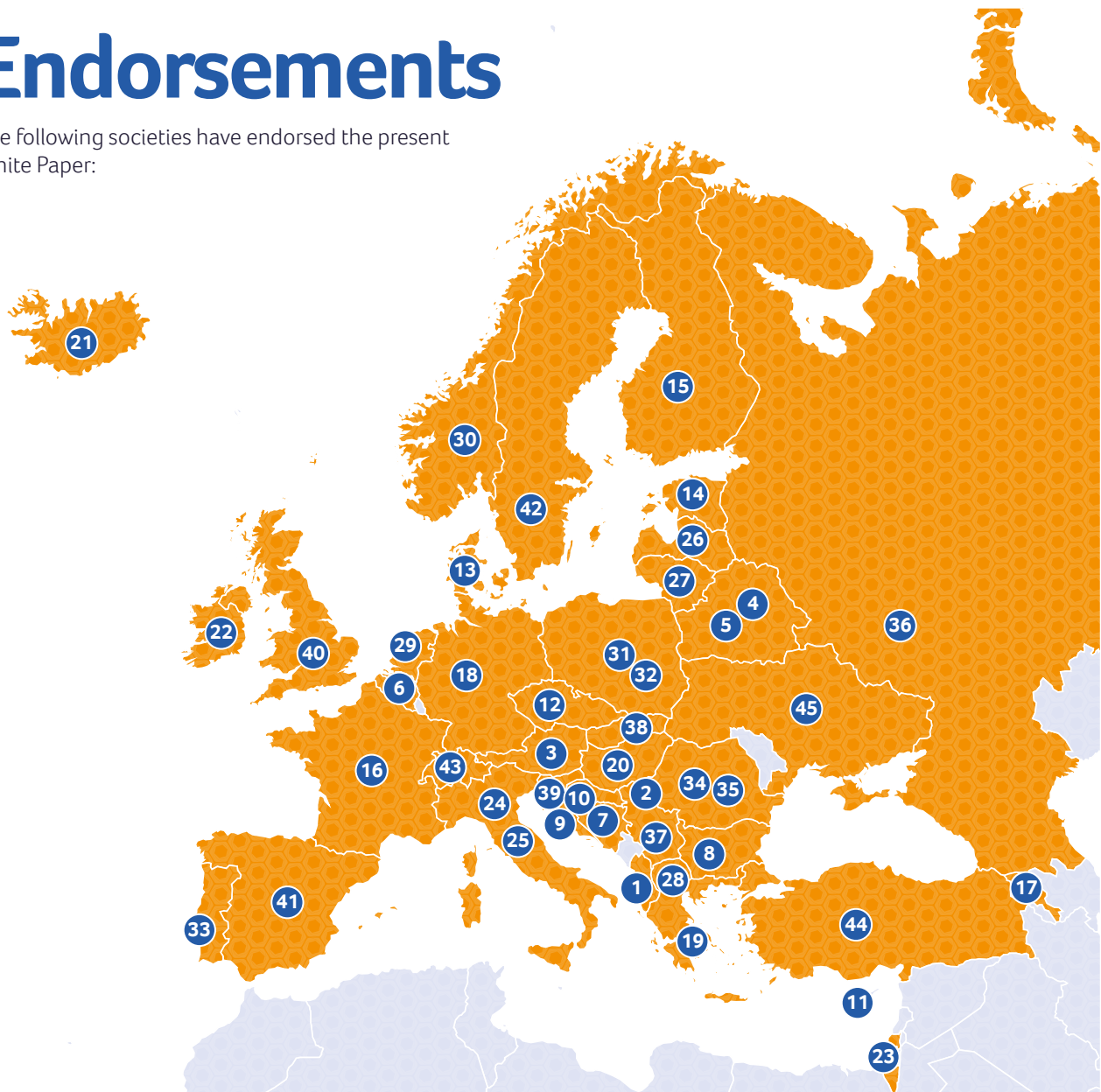
Collaboration across borders through ECAS

To properly represent the different aspects and stakeholders in endocrinology, ESE works with the ESE Council of Affiliated Societies (ECAS), a council with membership of 54 National Endocrine Societies across the wider geography of Europe.

ECAS provides a forum for discussions between the European Society of Endocrinology and its National Affiliated Societies about future projects, an opportunity for them to raise concerns and issues faced by their members and for the National Affiliated Societies to work together with the European Society of Endocrinology for the benefit of endocrinologists throughout Europe. The full ECAS membership can be found [here](#).

Endorsements

The following societies have endorsed the present White Paper:



- 1 Albanian Society of Endocrinology
- 2 [Association of Endocrinologists and Diabetologists of the Republic of Srpska](#)
- 3 [Austrian Society for Endocrinology and Metabolism](#)
- 4 Belarusian Association of Endocrinologists
- 5 [Belarusian Public Medical Society “Endocrinology and Metabolism”](#)
- 6 [Belgian Endocrine Society](#)
- 7 Bosnia and Herzegovina Society of Endocrinology and Diabetology
- 8 Bulgarian Society of Endocrinology
- 9 [Croatian Society for Endocrinology and Diabetology](#)
- 10 Croatian Society for Diabetes and Metabolic Disorders
- 11 Cyprus Endocrine Society
- 12 [Czech Endocrine Society](#)
- 13 [Danish Endocrine Society](#)
- 14 [Estonian Endocrine Society](#)
- 15 [Finnish Endocrine Society](#)
- 16 [French Endocrine Society](#)
- 17 [Georgian Association of Endocrinology and Metabolism](#)
- 18 [German Society for Endocrinology](#)
- 19 [Hellenic Endocrine Society](#)
- 20 [Hungarian Society of Endocrinology and Metabolism](#)
- 21 [Icelandic Endocrine Society](#)
- 22 [Irish Endocrine Society](#)
- 23 [Israel Endocrine Society](#)
- 24 [Italian Endocrine Society](#)
- 25 [Italian Association of Clinical Endocrinologists](#)
- 26 [Latvian Association of Endocrinology](#)
- 27 [Lithuanian Society for Endocrinology](#)
- 28 Macedonian Endocrine Association
- 29 [Netherlands Society for Endocrinology](#)
- 30 [Norwegian Society of Endocrinology](#)
- 31 [Polish Society of Endocrinology](#)
- 32 Polish Society of Gynecological Endocrinology
- 33 [Portuguese Society of Endocrinology, Diabetes and Metabolism](#)
- 34 [Romanian Psychoneuroendocrine Society](#)
- 35 [Romanian Society of Endocrinology](#)
- 36 [Russian Association of Endocrinologists](#)
- 37 Serbian Endocrine Society
- 38 [Slovak Endocrine Society](#)
- 39 [Slovenian Endocrine Society](#)
- 40 [Society for Endocrinology, UK](#)
- 41 [Spanish Society of Endocrinology and Nutrition](#)
- 42 [Swedish Endocrine Society](#)
- 43 [Swiss Society of Endocrinology and Diabetes](#)
- 44 Society of Endocrinology and Metabolism Turkey
- 45 Association of Endocrinologists of Ukraine

Collaboration across the different areas of endocrinology – ESE and Specialist Affiliated Societies

ESE also works together with the ESE Specialist Affiliated Societies, representing specific areas of endocrinology. A Specialist Society is a pan-European or international endocrine society with specific focus on a sub-specialty of endocrinology. ESE maintains privileged relationships with the below Specialist Affiliated Societies, which have all endorsed the present White Paper.



European Academy of Andrology (EAA)

Purpose of the Society: EAA is a non-profit international society of scientists and clinicians promoting research and education in andrology, a biomedical field which covers all aspects of male reproductive and sexual health, and male-specific diseases.

Key policy areas of importance to the Society:

- Establish EAA-certified training and research centres in andrology in Europe and beyond;
- Create a pan-European medical subspecialty in andrology;
- Improve research in the field of male reproductive and sexual function (and dysfunction);
- Disseminate knowledge in the field of andrology through the European Congress of Andrology and educational activities
- Increase public awareness in the area of male health.

Website: <https://www.andrologyacademy.net/>



European Calcified Tissue Society (ECTS)

Purpose of the Society: ECTS is a volunteer-led, not-for-profit scientific society promoting excellence in research into the field of calcified tissues within Europe, and committed to ensuring that the findings are disseminated to enable benefit to patients with metabolic bone disease.

Key policy areas of importance to the Society:

- Advance scientific knowledge and improve clinical practice in the field of osteoporosis and other diseases affecting skeletal health by providing educational opportunities and exchanges with a multidisciplinary and international approach;
- Provide research and clinical practice guidance in matters of public and professional interest in calcified tissues and related subjects in Europe. For example, we emphasise the importance of Vitamin D for bone health and we provide recommendations on adequate doses;
- Improve the research, diagnosis and treatment of the 400+ rare bone diseases by partnering and supporting the European Registry for Rare Bone and Mineral Conditions (ERN-BOND), the European Registry for Bone and Mineral Conditions (EuRR-Bone) and the European Rare Bone Forum (ERBF).

Website: www.ectsoc.org





European Network for the Study of Adrenal Tumors (ENS@T)

Purpose of the Society: ENS@T is a scientific society working on improving the understanding of the genetics, tumorigenesis and hypersecretion in patients with adrenal tumours and associated familial syndromes. It is committed to improving the prediction of recurrence and the management of malignant adrenal tumours.

Key policy areas of importance to the Society:

- Continue work on the ENS@T databases for adrenocortical adenoma (ACC), aldosterone producing adenoma (APA), non-aldosterone producing adrenal cortical adenoma (NAPACA) and Pheo acting as a core dataset for each tumour entity as a minimum work-up requirement;
- Further engage with existing and future clinical studies including EURINE-ACT (diagnostic and prognostic value of urine steroidobolomics in patients with adrenocortical tumours) and ADIUVO (a prospective, randomized, open-label, controlled, phase III trial for patients with ACC after radical resection);
- Develop clinical guidelines;
- Maintain and improve ENS@T centres of excellence;
- Coordinate EU funded research consortia, including ENS@T-ht (ongoing) and ENS@T-Cancer (finalised 2016).

Website: www.ensat.org



European Neuro-Endocrine Association (ENEA)

Purpose of the Society: ENEA is a scientific society promoting the integration of neuroendocrinology in all its aspects, through basic, translational, and clinical research throughout Europe and beyond. ENEA focuses on basic and clinical research in neuroendocrine physiology, pathophysiology, oncology and therapeutics as well as in disciplines affected by neuroendocrinology like metabolism and psychiatry.

Key policy areas of importance to the Society:

- Improve the diagnosis and therapy of patients with change to: pituitary tumours and other neuroendocrine pathologies in an international, interdisciplinary and scientific context;
- Coordinate research at European hospitals and health research institutes, with emphasis on basic and clinical research for the diagnosis and treatment of pituitary tumors, pituitary diseases and neuroendocrine pathologies;
- Offer education and training for physicians and scientists at annual scientific and educational meetings.

Website: www.eneassoc.org



European Society for Paediatric Endocrinology (ESPE)

Purpose of the Society: ESPE is an international society based in Europe that promotes the highest levels of clinical care for infants, children and adolescents with endocrine conditions throughout the world, including in less advantaged areas, by stimulating and supporting research and education.

Key policy areas of importance to the Society:

- Improve the work on rare endocrine diseases as most paediatric endocrine conditions are rare. ESPE and members are very active in Endo-ERN, via collaborative guidelines and projects and case discussions via the clinical patient management system (CPMS);
- Support research on obesity to get more insight into adiposity programming, factors driving the increasing prevalence and testing treatment options. Fellows-in-training receive education during the annual ESPE Diabetes and Obesity school;
- Support research and education on Endocrine Disrupting Chemicals. Several ESPE member groups are EDC experts.

Website: www.eurospe.org



European Thyroid Association (ETA)

Purpose of the Society: The ETA is a scientific organisation, which aims to promote clinical and basic research and raise the standards of understanding and clinical practice in thyroid disease.

Key policy areas of importance to the Society:

- Support research and education in Europe in the field of thyroidology to gather more insights into the pathogenesis of thyroid diseases;
- Provide education in the field of clinical, translation and basic thyroidology to our junior members, through Research Grants, consolidate co-operation and collaboration among clinical and basic thyroidology departments within Europe, and offer to our members, high-standard annual meetings and other educational activities during the academic year;
- Improve thyroid cancer diagnostics and treatments by supporting the ETA-Cancer Group as well as share knowledge and experience with investigators and clinicians from other medical associations that also place a strong focus on thyroid cancer;
- Formulate a petition addressed to the European Commission stressing the necessity to acknowledge thyroid diseases as non-communicable diseases. To this end, the ETA will collaborate with ESE.

Website: www.eurothyroid.com



Growth Hormone Research Society (GRS)

Purpose of the Society: The GRS consensus academic society acts as an independent, non-profit society that facilitates and evaluates advances in the physiology, pathology, diagnostics, therapeutics and surveillance of growth hormone (GH) and insulin-related growth factor (IGF)-related disorders.

Key policy areas of importance to the Society:

- Promote scientific research and clinical advancement in the fields of growth hormone (GH) and insulin-like growth factors (IGFs);
- Foster collaboration between scientists, clinicians (paediatric and adult) and clinical investigators from both the public and private sectors to promote research;
- Convey knowledge through the Society's journal, scientific meetings and workshops.

Website: www.ghresearchsociety.org/GRS_consensus.htm



Endo-ERN

European Reference Network
on Rare Endocrine Conditions

European Reference Network on Rare Endocrine Conditions (Endo-ERN).

This White Paper was endorsed by the European Reference Network on Rare Endocrine Conditions (Endo-ERN). The main objective of Endo-ERN is to reduce and ultimately abolish inequalities in care for patients with rare endocrine conditions in Europe, through facilitating knowledge sharing and high quality healthcare and research.

To find out more about ESE and our network please visit:
www.eese-hormones.org

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Annex

Relation of hormone and functions they control

Functions controlled by hormones	Most important hormones involved
Growth: stature, cell and tissue growth	Growth hormone Thyroid hormones Sex steroids (androgen, estrogen) Growth Factors
Reproduction: Puberty, sexual behaviour, fertility Pregnancy, child birth, lactation	Pituitary hormones (LH, FSH) Sex steroids (androgen, estrogen) Neurotransmitters and catecholamines involved in emotion, pleasure and drive Placenta hormones (hCG, estrogens) Oxytocin Prolactin
Energy intake and expenditure: hunger and satiety, tissue metabolism	Insulin, leptin, ghrelin and other gut hormones Peptides of the CNS Thyroid hormones
Regulation of blood sugar: response to hypoglycemia and acute stress	Insulin Glucagone Catecholamines Glucocorticoids Growth hormone Thyroid hormones
Regulation of water balance and blood pressure: loss or overload of liquids, ion equilibrium, vasoconstriction, vasodilation, heart rate	Vasopressin Aldosterone Renin, angiotensin Atrial natriuretic peptide Catecholamines Endothelins Nitric oxide (NO)
Regulation of Calcium and Phosphorus: Neuromuscular transmission, muscle contraction, bone structure, nucleic acids, signal transduction	Vitamin D Parathyroid hormone Calcitonin

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