

Issue 52 Winter 2023

# Endocrine Views

Opinion and news from the European Society of Endocrinology

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## Stockholm welcomes ECE 2024

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Meet your new President

How safe is testosterone replacement?



European Society  
of Endocrinology





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# Editorial



As the end of 2023 approaches, we look forward to next spring and the European Congress of Endocrinology in Stockholm, Sweden. The deadline for submission of abstracts is 22 January, so send yours as soon as possible. You can find out more about ECE 2024 on pages 3 and 7.

This issue of *Endocrine Views* is packed with research, opinion, debate and more. Dimitrios Goulis gives us an insight into current understanding of the safety of testosterone replacement in middle-aged and older men on page 9. Meanwhile, Helena Teede and Joop Laven discuss the latest crucial guidance for the management of PCOS on page 10. Alterations in thyroid function have been reported in obesity and, on page 11, Giorgio Radetti and Mario Rotondi consider the underlying relationship.

We present two sharply contrasting opinions on a role for the androgen receptor (AR) in treating oestrogen receptor-positive breast cancer: Theresa Hickey and Wayne Tilley argue that AR stimulation is the appropriate approach, while Jennifer Richer and Anthony Elias argue for AR inhibition. Read both perspectives on page 8.

*European Journal of Endocrinology* and *Endocrine Connections* have also provided us with a rich seam of interesting science. Our 'Editors' Selection' for this issue highlights recent papers on a link between adolescent obesity and cognitive performance (Maya Simchoni and Gilad Twig, page 12), oxytocin and avoidant/restrictive food intake (Anna Aulinas and colleagues, page 14) and cardiovascular risk factors after cancer (Nikolaos Kyriakakis and Robert D Murray, page 15).

I have finally come to the end of my term as Editor of *Endocrine Views*. Much has changed since I first joined the Editorial Board, and I am particularly proud of the magazine's recent development into a forum for discussion, which highlights the most important issues in our field. Indeed, this is also the last issue that will appear in print; the next one will be digital-only, heralding even greater interactivity and connections with other media.

On your behalf, I welcome Marek Bolanowski as the next Editor, and Eleni Armeni to the new role of Deputy Editor. I hope they enjoy the opportunity to publish articles of interest to you, the ESE membership, as much as I have.

**Justo P Castaño**  
Editor, *Endocrine Views*

### Areas of interest in this issue:



Adrenal and Cardiovascular Endocrinology



Events



Publications



Diabetes, Obesity, Metabolism and Nutrition



Grants



Reproductive and Developmental Endocrinology



Endocrine-related cancer



Pituitary and Neuroendocrinology



Thyroid



# ECE 2024

26th European Congress of Endocrinology

Stockholm from the City Hall

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## ECE 2024 deadlines

Abstract submissions:

**22 January 2024**

Grant applications:

**15 March 2024**

Super Early Bird registration:

**25 March 2024**

Early Bird registration:

**22 April 2024**

[www.es-e-hormones.org/ece2024](http://www.es-e-hormones.org/ece2024)

# Come to Stockholm!

Don't miss the largest endocrine event in Europe: the European Congress of Endocrinology. ECE 2024 takes place in Stockholm, Sweden, on 11–14 May 2024.

On behalf of everybody on the Local Organising Committee (LOC), I extend a heartfelt invitation to you to the forthcoming 26th European Congress of Endocrinology (ECE 2024), in the captivating city of Stockholm. The meeting's hybrid format means you can enjoy joining us either in person or remotely with ECE@Home.

The COVID-19 pandemic means that our preparations have been diligently underway for some time, and we are very much looking forward to finally greeting you next May, when Stockholm unveils some of its most picturesque vistas.

Stockholm, the capital of Sweden, holds a rich historical legacy dating back to its establishment in 1252. The city is embraced by the gentle waters of Lake Mälaren to the west, while the expansive Baltic Sea archipelago graces its eastern shores. Linked by an intricate network of 57 bridges, Stockholm's 14 interconnected islands boast a remarkable landscape, where waterways make up 30% of the city's composition,

complemented by lush parks and verdant expanses.

Notable among the local attractions are Stockholm City Hall, renowned for hosting the prestigious Nobel Banquet beneath the gleaming Three Crowns atop its tower – a definitive emblem of Stockholm's identity. The historic Gamla Stan, or Old Town, stands as one of Europe's largest and best-preserved medieval city centres; it is the very birthplace of Stockholm. The Vasa Museum houses the beautifully preserved 17th-century warship Vasa, once the pride of the Swedish Crown, which, regrettably, met its fate on its inaugural voyage in 1628. Pioneering in its concept, the world's first open-air museum, Skansen, established in 1891, offers an immersive journey into Sweden's historical tapestry, complete with traditional dwellings and a showcase of the nation's diverse flora and fauna.

As the cultural, political and financial nucleus of Sweden, Stockholm boasts an intellectual eminence with internationally renowned institutions, including

the Karolinska Institutet, the Stockholm School of Economics and the Royal Institute of Technology. Epicurean explorers will find their desires met by Stockholm's array of Michelin-starred restaurants, a distinction amplified by its recognition as the European Capital of Gastronomy for 2023.

It is with great pride that we extend an open-armed invitation to our beloved hometown, and eagerly anticipate engaging in stimulating scientific dialogue with each of you.

**Charlotte Höybye**  
LOC Chair, ECE 2024

## Endocrinology in Sweden

Endocrinology boasts a venerable legacy in Sweden, dating back to 1746 when Carl von Linné, the architect of taxonomy, made an early mention of goitre. A pivotal moment in 1877 saw Ivar Sandström unveil the role of the parathyroid glands. With the dawn of the 20th century, Sweden continued to make significant contributions to endocrine research.

During the dynamic 1960s, Sixten Franzén, a visionary pathologist, introduced fine needle biopsies, a revolutionary technique that quickly spread globally. The neurosurgeon Lars Leksell developed stereotactic radiotherapy, culminating in the application of the Gamma Knife in 1968. In 1991, Olle Kämpe identified antibodies targeting 21-hydroxylase, with great diagnostic significance in Addison's disease.

The first endocrine clinic in Sweden was established in 1958 at the Karolinska University Hospital under the leadership of Rolf Luft, a visionary who also described the first mitochondrial disease, now aptly known as Luft's disease. It was within this institution that Kerstin Hall isolated somatomedin, unlocked the secrets of insulin-like growth factor (IGF)-binding protein-1, and developed radioimmunological methodologies for IGF analysis.

Further enriching this legacy, Viktor Mutt at the Karolinska Institute pioneered the isolation and characterisation of multiple endocrine peptides. Last but not least, Suad Efendic was among the first to study the anti-diabetogenic actions of glucagon-like peptide-1, while revealing somatostatin's dual role in pancreatic hormone synthesis and inhibition of carcinoid tumour activity.

From this scientific evolution sprung forth the Swedish Endocrine Society, an entity embodying collaboration and advancement. With a membership exceeding 400, the Society stands as a nexus for Swedish endocrinologists, converging to facilitate national gatherings, promulgate treatment guidelines and nurture the education of nascent endocrinologists and dedicated endocrine nurses. You can find out more about the Society at [www.endokrinologforeningen.se](http://www.endokrinologforeningen.se).



Drottningholm Palace, residence of the Swedish royal family



# New Editor and Deputy Editor for *Endocrine Views*

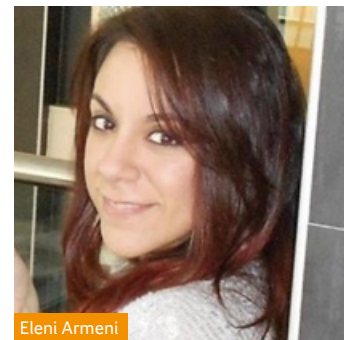
Marek Bolanowski (Poland) and Eleni Armeni (Greece/UK) have joined the Editorial Board of *Endocrine Views*. They will take on the roles of Editor and Deputy Editor respectively for issue 53 onwards, and were welcomed to their first Editorial Board meeting in September. Marek has agreed to be Editor for the next two years, after which Eleni will start a four-year term in the role. We very much look forward to working with them as they implement

exciting new developments for the magazine.

We are hugely indebted to retiring Editor Justo Castaño, who is stepping down after more than 12 years on the Editorial Board, the last four of which have been as Editor. Justo's vision has led to the magazine becoming a flagship for communication among members of the Society, in a format which is increasingly integrated with other ESE channels, including social media.



Marek Bolanowski



Eleni Armeni

## Endocrine Views goes virtual!

In a bid to lessen our environmental impact and reduce costs, this is the last issue of *Endocrine Views* to be printed on paper. Issue 53, to be published in Spring 2024, will arrive in your email inbox and herald increasing interactivity in your membership magazine. Watch out for your first digital-only magazine next March!



## Enhanced website for ESE



We are excited to unveil the new-look ESE website, which includes novel features to enhance its functionality and bring it right up to date. We hope you enjoy using it to find out even more about the benefits that ESE can bring you, its members!

## Funding for research into CAH

We are delighted to announce a new partnership with International Fundraising for Congenital Adrenal Hyperplasia (IFCAH), together with the European Society for Paediatric Endocrinology.

IFCAH's 2024 call for projects invites applicants to bid for financial support towards research into congenital adrenal hyperplasia (CAH). Selected research projects will receive up to €150,000 from a total fund of €350,000.

IFCAH is a private fund, created in 2010 by parents of children with CAH. Through its annual call for projects, IFCAH hopes to



contribute to the emergence of new therapeutics for the disease and its complications.

You can find full details at [www.ifcah.com/call-for-projects](http://www.ifcah.com/call-for-projects). Applicants should submit a letter of intent by 15 January 2024. Those whose projects are short-listed will be asked to submit a full application in April 2024.

We encourage ESE members to apply for this exciting opportunity!

## From the ESE Office

Exciting new improvements have kept us busy in the ESE Office. Some of the developments will be more visible than others, but all should have a very positive impact on your interactions with ESE.

The following three projects are all part of a digital transformation for ESE, which will help support our continuing development and our ability to support you, our members, in the best way possible.

First, you will have seen that we have developed and launched a new ESE website at [www.es-e-hormones.org](http://www.es-e-hormones.org). The previous one was launched in 2017, so an upgrade was due. We hope you like the fresh new look for ESE, with improved navigation, content organisation and searchability, so you can find the information that is important to you.

Our new customer relationship management (CRM) system will enable us to store data so that we can fully understand your needs as our members, and make sure we send you information that will interest you, based on your past activities. Development of the CRM has been a sizeable undertaking and investment for the Society, and a detailed and challenging piece of work (as anyone who has worked on similar projects will know). As a result, you can look forward to even smoother experiences than usual, in terms of membership applications and renewals, and grant and award applications, just to give a few examples. Please bear with us if we need to iron out a few wrinkles over the coming months, as the system settles into place.

We are also introducing a learning management system, to support the

delivery of our educational events, and to store the library of past events in a friendly and accessible way.

One reason for building the new CRM system is to enable us to bring membership handling in-house, and to have even better communication with our members. We are therefore further expanding the ESE Office Team in the areas of membership, marketing and finance, so we are hard at work on recruitment. Our association management company, Bioscientifica, has handled these activities for many years, and we thank them for their invaluable support!

It is an exciting time for ESE as we continue to develop and grow, to be even better positioned to support you all! As ever, do not hesitate to contact me with any questions.

Finally, I am very much looking forward to seeing all of you in



Stockholm at ECE 2024 – please submit your abstracts by 22 January.

**Helen Gregson**  
Chief Executive Officer, ESE  
[helen.gregson@ese-hormones.org](mailto:helen.gregson@ese-hormones.org)

## Keep up to date with ESE on social media



SEEndocrinology



EuropeanSocietyofEndocrinology



esehormones



European Society of Endocrinology



# Meet your new President

Jérôme Bertherat became President of ESE in May 2023. We took this opportunity to ask his thoughts on the future of endocrinology, current challenges facing endocrinologists, and how ESE can make a difference.

ESE is now 17 years old. It has grown tremendously in the last 10 years, in terms of members, very active committees and working groups, and a very efficient ESE Office Team.

ESE is already the constant voice of endocrinology in Europe and at the international level, but we must ensure this voice is further amplified, to promote endocrine education, health and research. We should be ready to support our community when facing any new difficulty: whether this takes the form of regulatory issues, drug shortages or a humanitarian crisis.

Attracting even more members remains a major goal, and is also the best sign that our activities benefit our community. Further growth has to be approached in an inclusive way in terms of geography within Europe and beyond, attracting both clinicians and researchers, various categories of healthcare professionals working with endocrine patients, patient advocacy groups and – of great importance for the future of endocrinology – early career members. Diversity and inclusivity are key!

## Facing the challenges to endocrinology

Despite hormones and various endocrine and metabolic disorders being well known, endocrinology, as a medical specialty or an area of research, is not clearly identified by the general population or the policymakers. ESE needs to continue to speak loudly to explain our discipline's importance in the wide range of common and rare medical conditions that are a burden to society, and in research. We must ensure students see our specialty as attractive. With all its members, the voice of ESE will make a difference!

## Helping to address societal problems

Regarding 'man-made' endocrine problems, we need to gather scientific evidence to understand the link between them and human collective behaviour. Endocrinologists have already collected much evidence in the

fields of endocrine disruption and obesity. Similarly, other scientists have demonstrated the effects of human activities on problems such as climate change and global warming, which was clearly visible last summer.

Man-made problems are linked, by definition, to human behaviour: both individual and collective change is needed in everyday activities to resolve them. But, as physicians, we know very well that changing a patient's behaviour to solve a health issue is difficult.

ESE can act at two levels:

(a) to provide the general public and policymakers with scientific evidence from our field and with educational messages, and (b) to evaluate its own activities to reduce endocrine-disrupting chemicals (e.g. plastic waste during meetings) and its carbon footprint (e.g. air travel, ECE venues).

## Building key relationships

The fact that endocrinology is multidisciplinary is both a strength and a weakness. Adult and paediatric endocrinologists must work together to benefit patient care and other disciplines. ESE will continue to maintain an interest in all aspects of endocrinology, interacting with the specialised societies that focus on specific areas. We must involve ourselves with groups comprising other specialists (surgeons, pathologists, radiologists, oncologists) who care for endocrine patients. We also need to watch carefully and lobby regarding regulatory aspects of medical practice that could concern endocrinology. With its policy and advocacy activities and extensive networking, ESE will raise the profile of our discipline.

## Minimising inequalities in healthcare

ESE has two targets to address inequalities in healthcare across Europe: policymakers and education. Reaching policymakers is a goal of our activities in Brussels. Education is clearly our everyday task: our online and face-to-face educational events and our publications aim to inform healthcare professionals and also patients. Providing access to the same level of information is a first, major step to reduce inequalities.

## Embracing change

Many new omics and mass spectrometry tools have been developed to investigate hormones and endocrine glands. In the next decade, their integration, along with the use of artificial intelligence, will lead to new diagnostic and therapeutic tools.

Meanwhile, in terms of epidemiology, we face an increasing burden of conditions such as obesity, diabetes and reproductive disorders, partly due to the 'man-made' problems discussed above. The use of new technology and educational approaches will make patients with chronic conditions more autonomous.

ESE will play a major role in stimulating positive developments and informing and educating its members about these novelties.

## A message for ESE members

ESE is our common 'home' and exists to support you, its members. The more of us there are, and the more active we are, the better the home will be. Please use all the networking opportunities that are offered by the many ESE activities to interact with our community and promote endocrinology.



## A few personal insights

### My favourite part of ECE...

Science and networking of course: diversity, quality and novelties of the scientific programme and opportunities to meet colleagues and friends, old and new!

### Area of research that is most intriguing...

I am tempted to become trained in artificial intelligence to see whether new answers to existing questions could be revealed.

### Best thing about being President (so far)...

Interacting with experienced and early career colleagues at the international level, all highly motivated by endocrinology. Seeing the energy of each ESE committee and working group in developing our activities. Learning from the ESE Office Team about the various activities that explain ESE's success story, and understanding the specific expertise of each team member.

### What to ask me in two years' time...

Did you enjoy being President and was it fun? Did you succeed in your aims? Did anything unexpected happen? What would you say if an ESE member asked if they should run for President?!

**'ESE is our common "home" and exists to support you, its members. The more of us there are, and the more active we are, the better the home will be.'**



## Increasing membership benefits

2012

20

benefits including

5 events

2023

35

benefits including

11 events

3 new awards

6 new grants\*

\*not including expansion of existing grants

# Membership fees for 2024

ESE's membership fees have remained unchanged since 2012. So that ESE can continue working with you all to shape the future of endocrinology and to provide you with an increasing range of valuable benefits, members voted at the 2023 Annual General Meeting to support an increase in fees from 2024.

Importantly, the new rates mean that you and others working in any area of endocrinology will still have access to our tiered membership fees. These include concessionary rates for people in low- and middle-income countries, as well as for members of our National Partner Societies ([www.eese-hormones.org/membership-national-societies](http://www.eese-hormones.org/membership-national-societies)), early career members, students, nurses and allied health professionals.

From 2024, members can also choose to support those eligible for

a concessionary rate by opting to pay the full fee.

You will receive your renewal notification soon. Check that your contact and membership category details are up to date now by logging into the members' area at [www.eese-hormones.org](http://www.eese-hormones.org).

The new rates will help secure a sustainable future for the Society's valuable work in improving science, knowledge and health across Europe and beyond. This means ESE can continue to provide you with the wide range of benefits, and grow and broaden our activities.

**'The new rates will help secure a sustainable future for the Society's valuable work.'**

	Standard rate	Concessionary rates		
		National Partner Society members (from high-income countries)	All members from middle-income countries	All members from low-income countries
Clinician/ Clinician Scientist/ Scientist	€130	€90	€70	€55
Early Career Clinician/ Clinician Scientist/ Scientist	€60	€35	€25	€20
Nurse/AHP	€60	€35	€25	€20
Early Career Nurse/AHP	€35	€20	€15	€10
Student	€35	€20	€15	€10

AHP, Allied Health Professional.

# EJE Rising Stars 2024

Participation in the EJE Rising Stars Mentorship Programme is awarded to individuals chosen by the Editors of *European Journal of Endocrinology* (EJE) because of their exceptional promise as future, independent, leading endocrine researchers, who have high potential to become Editors of the journal.

### Benefits of the programme

- Membership of the EJE Rising Star Reviewer Board for two years
- A dedicated mentorship programme for future EJE Editors
- A travel bursary to attend ECE and the EJE Editorial Board meeting.

### Why you should be an EJE Rising Star

Two participants from the 2022 programme explain why it has been so valuable to them:

### Apply now

Apply before 15 December 2023 to join the 2024 cohort of EJE Rising Stars when the next two-year programme begins next May. Find out more at

[www.eese-hormones.org/eje-rising-stars-ed-board](http://www.eese-hormones.org/eje-rising-stars-ed-board)

*'Being part of the EJE Rising Stars programme was very, very interesting. Behind every published paper there is a huge amount of work by the Editorial Board and reviewers, which I could observe in detail. I learned a lot, and I learned from the best in our field.'*

**Dan Niculescu, Romania**



*'This has been a unique and enjoyable privilege that fostered my pursuit of excellence and sharpened my critical thinking, boosting me to thoroughly analyse every article and its potential impact on the endocrine community.'*

**Elena Valassi, Spain**





# What's in store in Stockholm?

The Preliminary Programme for ECE 2024 is online now, bursting with highlights from the breadth of endocrinology.

Learn what you can look forward to at [www.ese-hormones.org/ece2024](http://www.ese-hormones.org/ece2024). You will find a full programme for delegates attending Stockholm in person, as well as a programme of live-streamed sessions that can be viewed in real time by people participating via ECE@Home. They will be able to ask questions and join discussions through the Congress virtual attendance platform.

In addition, ESE On Demand will provide recorded Congress content to all registered delegates, to watch at their convenience. Delegates who are ESE members will have ongoing access to this online Congress material, while delegates who are not members can view it for 60 days after the event.

For the first time, this year's Preliminary Programme is only available in digital format, so reducing ECE's environmental impact.



## Many Congress highlights

### European Hormone Day 2024

Activities following the annual awareness day on 24 April will help alert policymakers across Europe to the importance of hormones.

### European Women in Endocrinology (EUWIN)

A special session and networking opportunities will further EUWIN's work in supporting women in endocrinology.

### Dedicated sessions

Enjoy diverse events focused on key groups or interests, such as EYES (ESE Young Endocrinologists and Scientists), Nurses, UEMS (European Union of Medical Specialists), Endo-ERN, ESE Guidelines and joint sessions with other societies.

## ESE Award Lectures 2024

### Jens Brüning (Germany)

Geoffrey Harris Award  
Hypothalamic control of energy and glucose homeostasis

### Li Chan (UK)

European Journal of Endocrinology Award  
Title to be confirmed

### Panagiotis Anagnostis (Greece)

Clinical Endocrinology Journal Foundation Award  
Early menopause: is it a different entity than premature ovarian insufficiency?

### Kathrin Zopf (Germany)

European Endocrine Nurse Award  
Raising the profile of endocrine nurses

### Felix Beuschlein (Switzerland)

Transatlantic Alliance Award  
Primary aldosteronism – solutions, insights and challenges

### Gudmundur Johannsson (Sweden)

European Hormone Medal  
Mortality and morbidity in rare pituitary and adrenal endocrine disorders

### Clémence Blouet (France)

Jens Sandahl Christiansen Award – Basic Science  
Median eminence oligodendrocyte plasticity regulates neuroendocrine output, energy and glucose homeostasis

### Giuseppe Bellastella (Italy)

Jens Sandahl Christiansen Award – Clinical  
The use of sodium–glucose cotransporter type 2 inhibitors (SGLT-2i) in particular conditions such as reactive hyperinsulinaemic hypoglycaemia following gastrectomy

## Plenary lectures

We will welcome Nobel Laureate Sir Peter Ratcliffe to our Opening Ceremony, to deliver his plenary lecture. Our confirmed plenary speakers include:

**Sir Peter Ratcliffe (UK)**  
Hypoxia

**Stafford Lightman (UK)**  
The clinical importance of high resolution, automated, ambulatory measurement of tissue steroids

**Shanna Swan (USA)**  
The silent decline: unlocking the enigma of dropping sperm counts and fertility rates

**Constantine Stratakis (Greece)**  
From molecular biology to precision medicine in endocrine tumours: are we there yet?

**Patrik Rorsman (UK)**  
Focus on the pancreas

## ECE 2024 deadlines

Abstract submissions:  
**22 January 2024**

Grant applications:  
**15 March 2024**

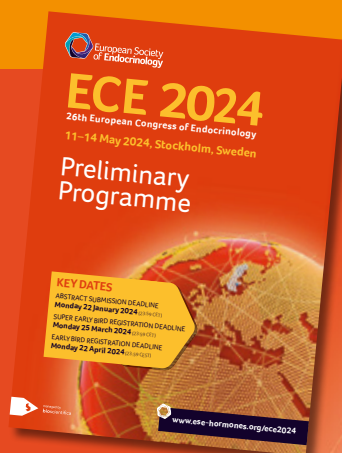
Super Early Bird registration:  
**25 March 2024**

Early Bird registration:  
**22 April 2024**

[www.ese-hormones.org/ece2024](http://www.ese-hormones.org/ece2024)

## Apply for an ESE grant

ESE members can apply for a Meeting Grant, Basic Science Meeting Grant or Nurse Grant (worth up to €400) to support the cost of attending ECE in person. See [www.ese-hormones.org/grants-and-awards](http://www.ese-hormones.org/grants-and-awards).





# A matter of debate



The contrasting opinions in this issue's debate centre on **the role of the androgen receptor (AR) in treating oestrogen receptor-positive (ER+) breast cancer**. Proponents of AR activation and supporters of AR inhibition each argue that their respective approaches will benefit patients with ER+ disease. The two sides of the presented debate are independent perspectives rather than mutually agreed positions.

We are honoured that representatives from leading groups on the two sides of the discussion have summarised the two points of view for us here: **Theresa Hickey and Wayne Tilley** from the University of Adelaide and **Jennifer Richer and Anthony Elias** from the University of Colorado.

By providing an insight into such carefully considered discussions in our field, we aim to keep endocrinologists up to date with the latest understanding, which has important implications for future research and patient care.

## In favour of AR stimulation

The AR is expressed in most primary (>90%) and metastatic (~70%) ER+ breast cancers.<sup>1</sup> Despite higher expression in ER+ tumours compared with normal breast tissues, the AR is not a disease driver. Rather, higher levels of AR independently predict better overall survival.<sup>1,2</sup>

This contrasts with its role in prostate cancer, where it is the key oncogenic driver (like the role of the ER in breast cancer). In cancer, dysregulated AR or ER activity drives prostate or breast cancer growth respectively.

Notably, AR activity inhibits normal breast growth, evidenced by two extreme scenarios: (a) genetic males with loss-of-function AR mutations develop female-like breasts and (b) high-dose testosterone given to adult females undergoing a gender transition induces breast involution.

A recent study has revealed the dramatic molecular changes associated with testosterone-mediated breast involution in such individuals,<sup>3</sup> showing that AR activation induces an environment conducive to protection against carcinogenesis. Critically, the AR has been shown to have a tumour suppressor role in ER+ breast cancer, including early and advanced, therapy-resistant disease states, that remain driven by the ER in the presence or absence of oestrogen hormone.<sup>1</sup> This tumour-suppressive role aligns with historic clinical data where androgenic drugs had efficacy in treating ER+ breast cancers,<sup>4</sup> with anti-cancer effects similar to the anti-oestrogenic drug tamoxifen.<sup>5</sup>

Recently, a selective AR modulator (enobosarm), an AR agonist with potent growth inhibitory activity in ER+ breast cancer cells,<sup>1</sup> achieved an 80% clinical benefit rate (CBR) in a randomised phase 2 study of metastatic ER+ breast cancers with >40% AR positivity.<sup>6</sup> In all patients (AR>10%), the CBR at 24 weeks was 32% in the 9mg arm and 28.8% in the 18mg arm (NCT01616758; Palmieri *et al.*, manuscript under review).

Conversely, a single arm study of an AR antagonist (enzalutamide) in combination with a selective ER degrader (fulvestrant) in metastatic ER+/HER2- breast cancer failed to meet its prespecified primary endpoint as defined by CBR, with stable disease only noted.<sup>7</sup>

Thus, there is strong evidence to support AR as a beneficial factor in ER+ breast cancer, and AR activation as a rational approach to managing this disease, which warrants testing in phase 3 clinical trials.

**Theresa E Hickey and Wayne D Tilley**

Dame Roma Mitchell Cancer Research Laboratory, Adelaide Medical School, University of Adelaide, Australia

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## In favour of AR inhibition

### Preclinical evidence

- In postmenopausal women, ER+ breast cancer is largely driven by oestrogens generated by the enzyme aromatase, which is blocked by aromatase inhibitor (AI) therapy.
- In the context of low-to-no oestrogen, the AR agonist dihydrotestosterone stimulates growth of ER+ breast cancer<sup>1,2</sup> and AR can substitute for ER to provide survival signals,<sup>1-3</sup> much as it has been shown to do in triple-negative breast cancer, where ER is absent.
- Inhibition of AR nuclear localisation decreases ER chromatin binding.<sup>2</sup>
- Elevated AR levels and activity support anchorage-independent growth and survival of cancer stem cell populations.<sup>3,4</sup>
- In prostate cancer, active AR in T cells limits immune checkpoint blockade efficacy.<sup>5</sup>
- In breast cancer, we and others find that AR regulates immune-suppressive factors. Using serial biopsies from clinical trials described below, early evidence suggests that anti-androgens may reactivate the immune system.

### Clinical evidence

- In the adjuvant endocrine treatment of ER+ breast cancer, high AR protein levels relative to ER (nuclear AR:ER ratio  $\geq 2.0$ ) associate with poorer disease-free survival.<sup>1</sup>
- In a clinical trial (NCT02953860) for women with heavily pretreated metastatic ER+ breast cancer unselected for the level of AR expression, combination fulvestrant plus enzalutamide achieved a 25% clinical benefit rate at 24 weeks.<sup>6</sup> In a randomised neoadjuvant trial (NCT02955394) for ER+ primary breast cancer (>T2), 4 months of combination fulvestrant plus enzalutamide resulted in a PEPI score 0 of 24.2% compared with 7.7% in the fulvestrant-only arm ( $P=0.16$ ) (AACR 2023, manuscript in preparation).
- In a randomised phase II study of patients with ER+ metastatic disease comparing the AI exemestane alone or with enzalutamide,<sup>7</sup> the cohort without prior endocrine therapy showed a numerical advantage in progression-free survival (PFS) for addition of enzalutamide in women whose primary tumours expressed high AR and low *ESR1*, and these patients had reduced risk of progression or death (HR 0.24,  $P=0.0011$ ), with median PFS extended by 10.2 months.

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# How safe is testosterone replacement?

Dimitrios Goulis examines the latest understanding of the cardiovascular safety of testosterone replacement in middle-aged and older men.

The classical types of hypogonadism include hypergonadotrophic hypogonadism (e.g. Klinefelter syndrome) and hypogonadotrophic hypogonadism (e.g. Kallmann syndrome). In addition to these, many symptoms and conditions (such as those caused by low testosterone concentrations in men with pituitary or testicular disease) become more common with increasing age and the presence of co-morbidities. When confirmed by appropriate testosterone assays, this is referred to as functional or late-onset hypogonadism (Figure). From an epidemiological point of view, this condition is very important.

EMAS (the European Male Ageing Study)<sup>1</sup> surveyed a random population sample of 3369 men between 40 and 79 years of age at eight European centres, by means of questionnaires and collecting data regarding general, sexual, physical and psychological health. According to EMAS, the prevalence of hypogonadism in middle-aged and older men is 2.1%. This means that, for every million of the population, you would expect 25 men with Kallmann syndrome (prevalence 1:20,000 in the general male population), 500 with Klinefelter syndrome (prevalence 1:1000 in the general male population, of whom <50% will be diagnosed), and at least 5000 with age-related hypogonadism (prevalence 2:100 in the middle-aged and elderly male population).

Testosterone replacement therapy (TRT) is the cornerstone of treatment for men with any type of hypogonadism. Efficacy and safety are the two main pillars of every treatment approach. Two key studies have evaluated these features. The TTrials (Testosterone Trials) were the main studies to focus on TRT efficacy. Very recently, the puzzle was completed by the TRAVERSE trial (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men), which focused on TRT safety.

## Efficacy

The TTrials (subdivided into Sexual Function, Physical Function and Vitality Trials)<sup>2</sup> assigned 790 men (age  $\geq 65$  years) with a serum testosterone concentration  $< 275$  ng/dl (9.5 nmol/l) and suggestive symptoms to receive either testosterone gel or placebo gel for one year.

TRT increased serum testosterone concentrations to the mid-normal range for men aged 19–40 years. The increase was associated with increased sexual activity (assessed by the Psychosexual Daily Questionnaire), sexual desire and erectile function. The percentage of men who increased their walking distance ( $> 50$  m in the 6-minute test) did not differ between the groups in the Physical Function Trial but did differ when men in all three trials were included (20.5% of men on TRT versus 12.6% on placebo,  $P=0.003$ ). TRT had no benefit regarding vitality (Functional Assessment of Chronic Illness Therapy – Fatigue scale).

In conclusion, in men aged  $\geq 65$  years with symptoms of hypogonadism, TRT was of moderate benefit to sexual function and some benefit to mood and depressive symptoms, but no benefit to vitality or walking distance.

## Safety

The TRAVERSE study<sup>3</sup> was a multicentre, randomised, double-blind, placebo-controlled, non-inferiority, clinical trial. It enrolled 5246 men (age range 45–80 years), who had pre-existing or a high risk of cardiovascular disease and confirmed hypogonadism (symptoms plus two fasting testosterone concentrations of  $< 300$  ng/dl (10.4 nmol/l)). The men were randomised to receive daily transdermal 1.62% testosterone

### Middle/advanced age hypogonadism

#### Synonyms

Late-onset hypogonadism  
Functional hypogonadism

#### Prevalence

(per million of the general population)  
5000 Middle/advanced age  
500 Klinefelter syndrome  
25 Kallmann syndrome

#### Diagnosis

Symptoms (mainly sexual)/Signs plus

Low serum testosterone (morning, fasting sample, validated assay):

- Total testosterone
- Calculated free testosterone (by sex hormone-binding globulin)

#### Causes

- Ageing
- Drug-induced
- Marijuana abuse
- Alcohol abuse
- Chronic systemic disease
- Acute or critical illness
- Organ failure
- Glucocorticoid excess
- Obesity
- Type 2 diabetes mellitus
- Sleep apnoea
- Malnutrition
- Excessive exercise
- Iatrogenic

#### Treatment

- Lifestyle changes
- Weight reduction
- Drug withdrawal/modification
- Testosterone gel/testosterone ester injections

#### Testosterone replacement therapy contra-indications

- Untreated prostate cancer
- Breast cancer
- Severe lower urinary tract symptoms (IPSS  $\leq 19$ )
- Severe heart failure (NYHA III/IV)
- Recent major cardiovascular event
- Polycythaemia
- Fertility desire

#### Follow-up

- History/physical examination
- Full blood count
- Liver enzymes
- Lipid profile
- Prostate-specific antigen
- Total testosterone
- Bone mineral density

IPSS: International Prostatism Symptom Score  
NYHA: New York Heart Association

gel (dose adjusted to maintain concentrations between 350 and 750 ng/dl (12.1–26.0 nmol/l)) or placebo gel.

The primary endpoint was the first occurrence of any component of a composite outcome (death from cardiovascular disease, non-fatal myocardial infarction, non-fatal stroke), assessed in a time-to-event analysis. The mean ( $\pm$ standard deviation) duration of follow-up was  $33.0 \pm 12.1$  months.

A primary outcome event occurred in 182 men (7.0%) in the testosterone group and 190 men (7.3%) in the placebo group (hazard ratio 0.96, 95% confidence interval 0.78–1.17,  $P < 0.001$  for non-inferiority). Similar findings were observed in sensitivity analyses in which data on events were censored at various times after discontinuation of testosterone or placebo. A higher incidence of atrial fibrillation, acute kidney injury and pulmonary embolism was observed in the testosterone group.

The study concluded that, in men with hypogonadism and pre-existing or a high risk of cardiovascular disease, TRT was non-inferior to placebo concerning the incidence of major adverse cardiac events.

## In conclusion

Based on evidence from the TTrials and TRANVERSE study, TRT is an effective and safe option for men with hypogonadism. Of course, as for every treatment, the successful approach is based on four pillars:

- Select the right patient (the one with confirmed hypogonadism).
- Inform him appropriately and involve him in the decision-making.
- Monitor him (clinical and laboratory evaluation at appropriate intervals).
- Collaborate with health professionals (for dose adjustments and prevention/treatment of adverse effects).

Despite the results discussed above, more data are needed regarding TRT efficacy and, especially, safety on additional outcomes (e.g. urogenital, bone, neoplasia, pulmonary). Nothing can be taken for granted until proved by high quality data. Pathophysiology is an excellent tool to generate research hypotheses and explain the results, but only evidence-based medicine can generate new knowledge. Endocrinology does not cease to surprise us!

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# PCOS: the latest guidance

Updated guidance for the management of polycystic ovary syndrome (PCOS) has recently been published in *European Journal of Endocrinology*.<sup>1</sup>

PCOS poses a global health challenge as a chronic endocrinopathy affecting 12% of women.<sup>1–3</sup> As a complex syndrome, it is neither a primary ovarian disease nor involves pathological ovarian cysts, with the historical misnomer arguably hindering advancement of understanding, recognition, research, care and, ultimately, health outcomes for those affected.<sup>1,4</sup>

It is caused by genetic interaction with metabolic and endocrine factors, manifesting with cardiometabolic, reproductive, psychosocial and dermatological features,<sup>5</sup> which vary within and between individuals, necessitating patient-centred multidisciplinary care.<sup>1,2,6</sup> Reproductive (ovulatory disturbance, infertility and pregnancy complications), psychological (depression and anxiety symptoms, disordered eating and poor quality of life) and cardiometabolic features (obesity, type 2 diabetes, cardiovascular risk factors and increased cardiovascular disease) are notable.<sup>1,3</sup>

PCOS evidence–practice gaps remain, with delayed diagnosis, inconsistent and fragmented care, inadequate information provision, suboptimal lifestyle management and under-recognition of the broad features reported globally.<sup>1,3</sup> In addition to narrow perceptions as a fertility disorder, progress is hindered by a lack of medical and health professional education, limited dedicated models of care and, as a women's health condition, by inherent gender bias in research and clinical care.

## Guideline development

Through global collaboration, we have developed and are translating a comprehensive international evidence-based guideline ([www.monash.edu/medicine/mchri/pcos/guideline](http://www.monash.edu/medicine/mchri/pcos/guideline)) for diagnosis, assessment and treatment of PCOS, to improve the lives of those affected.<sup>1</sup>

Extensive health professional and patient engagement informed clinical questions. International society-nominated panels, including ESE, involved patients and experts from across the relevant fields.<sup>1</sup>

Best practice guideline development methods included evidence synthesis and meta-analysis to generate 52 systematic and three narrative reviews.<sup>1,3</sup> The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework incorporated this evidence, quality appraisal, feasibility, acceptability, cost, implementation and, ultimately, recommendation strength. The work was completed by an international advisory and project board and 52 guideline development experts, including patient representatives.

The Monash University-led Centre for Research Excellence in Women's Health in Reproductive Life, funded by the Australian National Health and Medical Research Council (NHMRC), partnered with ESE, the European Society of Human Reproduction and Embryology, the American Society for Reproductive Medicine and the Endocrine Society; 34 other organisations also collaborated. Evidence-based and consensus recommendations and clinical practice points were generated and peer review was completed via international collaborating organisations and public consultation. Outputs were independently approved by the NHMRC.<sup>3</sup>

## Diagnosis

Recommendations include that PCOS should be diagnosed using the International Evidence-based Guideline Diagnostic criteria,<sup>1</sup> which build on the consensus Rotterdam criteria. In adults, this requires two of:

- clinical/biochemical hyperandrogenism
- ovulatory dysfunction, and
- polycystic ovaries on ultrasound ( $\geq 20$  follicles per ovary) or elevated anti-Müllerian hormone (AMH) levels.

Exclusion of other causes is needed. Importantly, if irregular menstrual cycles and hyperandrogenism are present (70% of cases), ultrasound or AMH are not required in diagnosis.<sup>1</sup>

In adolescents, both ovulatory dysfunction and hyperandrogenism are needed and ultrasound and AMH are not recommended, with poor specificity and overlap with physiological pubertal features.

## Assessment and management

PCOS assessment and management encompass reproductive, metabolic, cardiovascular, dermatologic and psychological features. Reproductive health plans are recommended, including healthy lifestyle, prevention of excess weight gain, optimisation of fertility, family planning, and screening and management of preconception and pregnancy risk factors. Metabolic risk factors, diabetes, cardiovascular disease and sleep disorders are increased in PCOS, with recommended screening and management.<sup>1</sup> PCOS should be considered a high risk condition in pregnancy, with women identified and monitored: an important new recommendation. Increased premenopausal endometrial cancer should be recognised. However, as absolute risks are low, routine screening is not recommended.

Anxiety and depressive symptoms are markedly increased and all should be screened, followed by assessment and therapy as indicated.<sup>1</sup> Greater awareness of psychological features, including eating disorders, impacts on body image and quality of life, is needed. Global surveys consistently report dissatisfaction with PCOS diagnosis and care, and raised awareness and education are strongly recommended for women and healthcare professionals, including high quality, evidence-based resources. Shared decision making and self-empowerment are fundamental, and integrated models of care are recommended.<sup>1</sup>

Supported healthy lifestyle is recommended in PCOS for overall health, preventing excess weight gain and, where indicated, optimising weight management. Recognising the benefits of a healthy lifestyle through a variety of healthy diets and physical activity approaches, no single lifestyle regimen is recommended. Weight bias and stigma should be minimised, and healthcare professionals should seek permission to weigh women, and explain weight-related risks.

## Pharmacological and other treatments

Combined oral contraceptive pills (COCPs) are first-line pharmacological treatment for menstrual irregularity and hyperandrogenism, with lower dose COCP preparations and minimal side-effect preparations recommended.<sup>1</sup> Metformin is recommended for metabolic features with greater efficacy than inositol, which offers limited clinical benefits in PCOS. Metformin is not routinely recommended in pregnancy and PCOS.

Laser therapy is effective for hair reduction in many subgroups.<sup>1</sup> Anti-androgens have a limited role where other therapies are ineffective (e.g. after 6–12 months of COCP), and require concomitant contraception. Anti-obesity agents and bariatric/metabolic surgery may be considered based on general population guidelines, balancing potential benefits and side effects, with greater research needed.

In infertility treatment, letrozole is first-line pharmacological management; alternatively, clomiphene can be used with metformin or alone. Gonadotrophins or ovarian surgery have a role as second-line therapies. In the absence of an absolute indication, and where other ovulation induction therapies have failed, *in vitro* fertilisation, potentially with *in vitro* maturation, is third-line therapy in women with PCOS and anovulatory infertility.<sup>1</sup>

## In conclusion

Overall, evidence in PCOS is low to moderate quality.<sup>3</sup> Given the high prevalence and significant health impacts, greater priority, funding and research are recommended. Guideline translation is extensive, including education outputs and resources such as AskPCOS ([www.askpcos.org](http://www.askpcos.org)).

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# Obesity and the thyroid gland

How should we interpret the alterations of thyroid function and structure that are found in patients with obesity?

Alterations in thyroid function have frequently been reported in patients with obesity, and have been suggested as a cause that favours weight gain. It would seem quite logical, since body composition and thyroid hormones are closely related, the latter being strongly involved in the process of energy expenditure by regulating basal metabolism and thermogenesis, lipid and glucose metabolism, food intake and fat oxidation.

Thyroid hormones and thyrotrophin (TSH) concentration have been variously described as normal, elevated or even low in adult subjects with obesity. Mild elevation (<20mU/ml) of serum TSH with thyroid hormones in the normal range (subclinical hypothyroidism) has also been reported in children with obesity.

## Possible mechanisms for altered function

Several mechanisms leading to hyperthyrotrophinaemia have been hypothesised. These include increased leptin-mediated production of pro-TSH-releasing hormone, impaired feedback due to a reduced number of tri-iodothyronine (T3) receptors in the hypothalamus and variations in peripheral deiodinase activity.

A further cause might be the low grade chronic inflammatory state that characterises obesity. In obesity, in fact, the adipose tissue secretes a distinct quantity of inflammatory cytokines, and some of these (such as tumour necrosis factor- $\alpha$ , interleukin-1 (IL-1) and IL-6) escape into the general circulation, provoking systemic symptoms. These cytokines have been proven to inhibit sodium/iodide symporter mRNA expression and iodide uptake activity in Fisher rat thyroid cell line (FRTL-5) and human thyroid cells. Their secretion might contribute to the compensatory increase in TSH levels commonly observed in obesity.

Of note, abnormalities in thyroid function and TSH mostly normalise following weight loss, independent of whether the loss is obtained by diet or bariatric surgery, suggesting that these biochemical alterations are reversible and therefore not secondary to thyroid cell destruction. This means that it is not the thyroid dysfunction that causes obesity, but exactly the contrary!

Animal studies demonstrating that mice fed an 8-week high fat diet experience a rise in TSH and reverse T3 levels would further support the above statement.

## Structural effects

In addition to these alterations in thyroid function, subjects with obesity who have negative tests for anti-thyroid antibody may also show an echographic pattern which is superimposable upon that seen in Hashimoto's thyroiditis (Figure). Our previous study<sup>1</sup> reported, for the first time, such changes in a group of children and adolescents who were either overweight or had obesity. To rule out the possibility of Hashimoto's thyroiditis without circulating anti-thyroid antibodies (which is possible in up to 15% of subjects), we also performed a fine needle biopsy in a group of them, which absolutely excluded the condition.

These results were confirmed by Rotondi in a group of adult patients.<sup>2</sup>

A possible explanation for the thyroid parenchymal changes could, again, be the presence of low grade inflammation, found in obesity. Inflammatory cytokines may induce vasodilatation and increased permeability in the thyroid vessels, leading to exudation of plasma. The subsequent parenchyma imbibition might explain the ultrasound findings.

## Reversibility of changes

To verify whether the observed changes in thyroid function and structure were absolutely functional and therefore reversible, we performed a prospective study in a group of children who were overweight or had obesity, and evaluated these parameters before and after weight loss.<sup>3</sup>

To do this, we selected 96 children with overweight or obesity, who did not have circulating anti-thyroid antibodies but who showed an altered thyroid function and structure at ultrasound. At baseline, body mass index (BMI), body composition, free thyroxine (FT4), TSH, high sensitivity C reactive protein (CRPs), white blood cells, metabolic profile and a thyroid ultrasound were assessed. Thyroid volume was calculated and alterations in echogenicity and homogeneity were recorded (thyroid score). The same parameters were reevaluated after a weight loss programme. We could observe, together with a significant decrease in BMI and body composition, also a significant decrease in CRPs, TSH and thyroid volume (all  $P < 0.0001$ ), while FT4 remained unchanged. The echographic pattern improved significantly, positively correlated to the weight loss, normalising completely in 50% of the subjects. BMI reduction was a unique predictor of the decrease in TSH, thyroid volume and improvement in the structure.

**‘The alterations of thyroid function and structure in children with obesity are reversible.’**

## Implications of these findings

The main outcome of the study was, therefore, that the alterations of thyroid function and structure in children with obesity are reversible, underlining the functional nature of the findings. Thus, no levothyroxine replacement treatment is suggested, while changes in lifestyle and dietary habits should be recommended.

As a final consideration, knowledge of this particular thyroid condition in subjects with obesity is very important, to avoid useless treatments and further diagnostics to exclude the presence of additional autoimmune diseases.

**Giorgio Radetti**

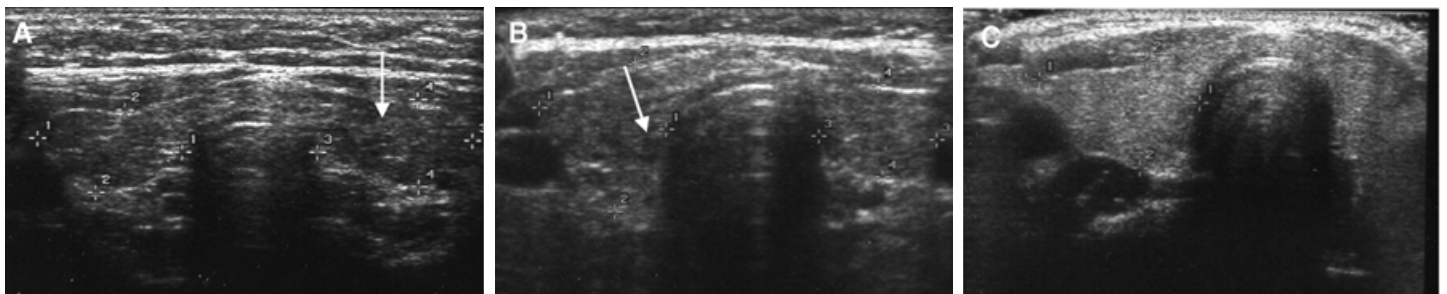
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Ultrasound images of the thyroid of (A) a subject with Hashimoto's thyroiditis, (B) a child with obesity and (C) a normal subject. Arrows show the hypoechoogenicity of the thyroid parenchyma. Reproduced by permission from Radetti et al.<sup>1</sup> ©2008 The Endocrine Society.



# EJE

# Adolescent obesity linked to cognitive performance

A recent article in *European Journal of Endocrinology* has examined the relationship between obesity and cognition in young people.<sup>1</sup>

The global spread of adolescent obesity over the past few decades has raised concern across multiple disciplines. While previous research mostly focused on cardiometabolic-related sequelae, scientists are now trying to uncover and explain another aspect of obesity – its relationship with cognitive performance.

At older ages, obesity has been suggested to accelerate cognitive decline and dementia. However, at younger ages, the association between obesity and cognition is under-researched, and the mechanisms involved are probably different.

Recently, we conducted a nationwide cross-sectional study to assess the relationship between body mass index (BMI) and cognitive performance in a sample of 2.48 million adolescents who were evaluated one year prior to mandatory military service, between 1967 and 2018.<sup>1</sup> Weight and height were measured, and cognitive performance was assessed using a validated IQ-equivalent test. Sociodemographic data regarding education and area of residence were noted. As these data were collected over five decades, we were able to account for parental cognitive performance that had been obtained in earlier years, for the parents as adolescents. Multinomial logistic regression models were applied.

## Our findings

We found that male adolescents with severe obesity had a significant disadvantage, with 29.4% of them scoring below the 25th percentile of cognitive score. In contrast, only 17.7% of their normal-weight counterparts fell into this lower-scoring category. There was a 'J-shaped' relationship regarding the odds for a low cognitive score across BMI categories. Notably, higher odds ratios for low cognitive scores were evident not only for men with severe obesity (OR 1.58 [1.52–1.64]), but also for those with underweight (OR 1.45 [1.43–1.48]). A similar pattern was observed in women.

Adjustment to sociodemographic factors or limiting analysis to those without any background illness (including neuropsychiatric morbidity) did not change the results. Findings were also consistent for all the subtests that constitute the cognitive score. For 445,000 individuals, parental cognitive performance was available, and allowed us to determine a range of expected cognitive score (depending on father/mother dominance). We observed that adolescents with abnormal BMI, but especially obesity, had higher odds of scoring less than the expected potential. The higher the adolescent BMI was, the higher were the odds of a greater negative deviation from the expected score. These observations were consistent in both sexes, even for adolescents without background illness.

## Discussion and conclusion

Several neurohormonal pathways may support an effect of obesity on cognition, including leptin signalling, insulin resistance, and the growth hormone and insulin-like growth factor-1 axis.<sup>2,3</sup> A genetic basis of common pathways and epigenetics-driven processes also support the association. Details of lifestyle factors, such as screen-time exposure, physical exercise and diet, among others, were unavailable, and may certainly also mediate the association. Given the cross-sectional nature



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of this study, it is inappropriate to refer to causality, especially as there is evidence that argues for a bidirectional association.<sup>4</sup>

The strengths of this study include unselected evaluation of cognitive performance and measurement of weight and height, together with systematic medical and socioeconomic data collection over a period of more than 50 years. Based on the previous literature regarding adolescent cognitive performance<sup>5</sup> and obesity<sup>6</sup> from this dataset, findings here could probably be generalised to other Western populations.

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## Insights from the Editor

This provocative and interesting study describes a J-shaped relationship between body mass index (BMI) and cognitive performance. In other words, either a high BMI (most likely to represent obesity) or a low BMI is associated with lower cognitive performance.

The study cannot establish whether these relationships are causal in either direction and, of course, there are multiple possibilities for confounding in this type of study. Nevertheless, it is noteworthy, because of the focus on adolescents, because of the huge scale of the dataset studied (nearly 2.5 million people) and because of the duration over which the data were gathered (more than 50 years). This gave the authors the opportunity to adopt multiple approaches to reduce the chances of confounding, including the opportunity to test associations with parental cognitive performance.

The findings are scientifically interesting, have relevance for public health, and are worthy of following up with confirmatory and mechanistic studies.

## Robert Semple

Deputy Editor, *European Journal of Endocrinology*

EJE Clinical & translational endocrinology from around the globe



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## New Editor-in-Chief for *Endocrine Connections*

We welcome Faisal Ahmed as the new Editor-in-Chief of *Endocrine Connections* from 1 January 2024.

Professor Ahmed has held the Samson Gemmell Chair of Child Health at the University of Glasgow, UK, since 2012, and is a consultant in paediatric endocrinology at Glasgow's Royal Hospital for Sick Children. Since 2019, he has also been Professor of Endocrine Registries at the University of Leiden, The Netherlands.



Faisal Ahmed

His research focuses on improving the care of people with rare endocrine conditions by developing strong partnerships and infrastructures to facilitate global translational research.

See <https://ec.bioscientifica.com/page/new-editor-in-chief> for an interview with Faisal Ahmed.

We thank Adrian Clark for his immense contribution to the journal during his term as Editor.



## Updated guidance on adrenal incidentaloma

ESE, in collaboration with the European Network for the Study of Adrenal Tumors (ENS@T), has undertaken a comprehensive revision of the 2016 ESE Clinical Practice Guideline on the management of adrenal incidentalomas. The new guidance reflects the most up-to-date understanding of the condition, so providing clinicians with practical guidance for patient care. It is available, with open access, in *European Journal of Endocrinology*. The guidance has also been endorsed by the Endocrine Society.

An information leaflet for patients has been produced in parallel with the guideline. You can find the guideline and leaflet along with all the other ESE Clinical Practice Guidelines at [www.e-se-hormones.org/guidelines](http://www.e-se-hormones.org/guidelines).



# EJE

# Oxytocin and avoidant/ restrictive food intake

This study, published in *European Journal of Endocrinology*, shows high levels of anorexigenic oxytocin in youth with avoidant/restrictive food intake disorder (ARFID).<sup>1</sup>



ARFID is a psychiatric disorder marked by insufficient dietary intake. In contrast to other eating disorders, individuals with ARFID do not experience body image concerns, but rather report heterogeneous reasons for avoidant/restrictive eating, such as lack of interest in food or eating, sensory sensitivity to food (texture, taste, smell) and/or fear of aversive consequences of eating (e.g. vomiting, abdominal pain, allergic reaction), leading to several clinical complications such as weight loss/failure to appropriately gain weight, nutritional deficiencies and low bone mineral density.<sup>2-4</sup>

Given the relatively recent introduction of ARFID as a psychiatric disorder to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), research to date is limited, and the pathophysiology of ARFID is not yet well understood.

## Anorexigenic oxytocin

Oxytocin is a hypothalamic-posterior pituitary neurohormone involved in a range of physiologic processes, including appetite suppression, which might be involved in the pathophysiology of eating disorders.<sup>5</sup> However, to date, no studies have investigated endogenous oxytocin levels in ARFID versus healthy controls.

## Oxytocin response to food intake in ARFID

We conducted a study to compare fasting and postprandial oxytocin levels in individuals with full and subthreshold ARFID ( $n=54$ ) and healthy controls ( $n=55$ ), with the hypothesis that levels of anorexigenic oxytocin would be higher in ARFID than in controls, given that those with ARFID report a low drive to eat. We also explored the impact of clinical characteristics – specifically sex (since oestradiol increases oxytocin release), age (since oxytocin levels may decrease with age) and body mass index percentile (since oxytocin levels may be weight-dependent) – on oxytocin levels among those with ARFID.

After obtaining a fasting blood draw, we instructed participants to consume a ~400kcal standardised mixed meal. Only those participants who ate >75% of the meal were included. We drew blood at 30, 60 and 120 minutes after the start of the meal. Serum samples were analysed for oxytocin.

We found that fasting and postprandial oxytocin levels were significantly higher at all time points in individuals with ARFID (compared with controls) independent of sex, age and body mass index percentile.

EJE Clinical & translational  
endocrinology from  
around the globe

## Conclusions

Given that a function of oxytocin is suppression of appetite, increased fasting and postprandial oxytocin levels in ARFID may contribute to low appetite and lack of interest in eating. Moreover, elevated oxytocin levels could represent an adaptive response to higher stress and/or fear, since oxytocin has well known anxiolytic properties and its secretion commonly increases following the presentation of fearful or stressful stimuli, such as the typically reported fear of gastrointestinal symptoms and/or food neophobia in some ARFID presentations.<sup>2</sup>

Interestingly, prior research suggests that conditioned taste aversion results in upregulation of oxytocin mRNA and protein expression in the amygdala in mice, and sensory aversions to food are common in ARFID, contributing to food avoidance.<sup>6</sup>

Taken together, our findings of consistently higher oxytocin levels in ARFID compared with controls provide support for a dysregulated oxytocin system that may be involved in the neurobiology and maintenance of ARFID. Further prospective studies will be important to determine whether altered oxytocin dynamics contribute to the development and maintenance of ARFID and establish whether oxytocin pathways could be targeted in treatment.

## Anna Aulinas

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## Jennifer J Thomas

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## Elizabeth A Lawson

Neuroendocrine Unit, Division of Endocrinology, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

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## Insights from the Editor

Oxytocin is a nine-amino acid peptide with anorexigenic effects. However, in anorexia nervosa, levels are lower than in healthy individuals, although postprandial patterns are similar to controls.

Avoidant/restrictive food intake disorder (ARFID) has only recently been formally recognised with diagnostic criteria in DSM-5, and is distinct from anorexia nervosa. It is defined by voluntary restriction of food intake without body image concerns. This study found high oxytocin concentrations in the ARFID group, which trended downwards after eating. This did not appear to be explained by body mass index, sex or age.

Though not the first finding of altered concentrations of satiety or appetite-related hormones in ARFID, it is the most strikingly abnormal finding to date. This tantalising early discovery suggests that oxytocin could play some role in the food aversive behaviour of ARFID. Further studies are required, both to replicate the finding and to test whether hyperoxytocinaemia is either a cause or consequence of this type of pathological eating behaviour.

## Robert Semple

Deputy Editor, *European Journal of Endocrinology*



# Cardiovascular risk factors after cancer

A pilot study in *Endocrine Connections* has examined cardiovascular risk factors in survivors of adult- and childhood-onset brain tumours.<sup>1</sup>

Increasing survival rates in patients with brain tumours, resulting from advancements in cancer treatment, have led to recognition that multimodality cancer therapy is associated with increased long term morbidity and late mortality. Although the excess mortality in survivors of childhood brain tumours (SCBT) primarily relates to recurrence or progression of the primary disease, these patients also have increased mortality related to cardiovascular and cerebrovascular disease, with standardised mortality rates of 4.2 and 4.6 respectively.<sup>2,3</sup> No equivalent data exist for brain tumour survivors of adult onset, probably due to the guarded prognosis of these individuals.

## Evaluation of cardiovascular risk factors

In this pilot, cross-sectional study, we evaluated cardiovascular risk factors in 36 long term survivors of primary malignant brain tumours of both adult and childhood onset, who had all undergone cranial radiotherapy. We compared these with individually age- and gender-matched controls.

Evaluation included weight and body composition analysis by bioimpedance, subcutaneous fat mass assessment (using Harpenden skin callipers), 24-hour blood pressure monitoring and biochemical investigations for fasting lipid profile, glucose metabolism (serum insulin and glucose) and insulin sensitivity using the homeostatic model assessment for insulin resistance (HOMA).

## Summary of key findings

The patients demonstrated adverse body composition with increased body mass index, waist circumference, total body fat mass and truncal fat mass. Subcutaneous fat mass was also higher, as measured by skinfold thickness. Additionally, patients had elevated total and low-density lipoprotein cholesterol levels, insulin and HOMA-insulin resistance, without differences in fasting serum glucose. No difference in blood pressure was observed between patients and controls.

There was no dichotomy in the prevalence of these risk factors between brain tumour survivors of adult or childhood onset: both patient subgroups, when examined individually against their respective controls, continued to exhibit a less favourable body composition, as well as higher cholesterol and HOMA-insulin resistance. However, differences in body composition were more pronounced for SCBT, who demonstrated an 84.1% increase in truncal fat mass compared with controls. In contrast, in patients with adult-onset brain tumours, truncal fat mass was increased by 41% compared with their controls.



## Further insights and future considerations

Hypothalamic insults due to tumour location, surgery, hypothalamic irradiation and endocrinopathies (particularly growth hormone deficiency, GHD) have been associated with the development of obesity in SCBT.<sup>4</sup> All patients in our cohort received high dose cranial radiotherapy leading to pituitary hormone deficits in most cases, particularly GHD. Notably, GHD is associated with adverse body composition, dyslipidaemia and insulin resistance,<sup>5,6</sup> and it has therefore been hypothesised that GHD may, at least in part, be implicated in the unfavourable metabolic profile of SCBT.<sup>7</sup> Whether GH replacement reverses the metabolic abnormalities previously described remains to be elucidated. However, previous research showed only minor improvements in body composition and lipid profile in adult survivors of childhood cancer of mixed aetiology with GH therapy.<sup>8</sup>

As survival of brain tumour patients continues to improve, adverse sequelae of cancer therapy will become more evident. For these individuals, the target has changed from simply surviving cancer to improving quality of life beyond cancer and managing long term complications.

Considering that endocrine- and metabolic-related late effects are highly prevalent in brain tumour survivors, the role of the endocrinologist in the monitoring and management of these individuals long term, as part of a multi-disciplinary team, is pivotal. Therefore, the results of this pilot study are highly relevant to clinical practice and warrant further study, especially in the population of brain tumour survivors of adult onset, which is currently an under-studied field.

**Nikolaos Kyriakakis and Robert D Murray**

Leeds Centre for Diabetes & Endocrinology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

## Insights from the Editor

In 1971, US President Richard Nixon launched a 'War on Cancer' – an event often considered as the start of the remarkable series of global discoveries which have led to improved treatments for this disease.

Half a century later, the benefits are widely seen. Brain tumours, often thought of as a death sentence in 1971, are now often treatable and curable, especially in childhood. However, as with most successful cancer treatments, there are longer term consequences. In recognition of this, *Endocrine Connections* recently launched a series of review and research articles on late effects of cancer treatment (<https://ec.bioscientifica.com/page/lateeffects>).

The study featured here demonstrates that brain tumour treatment almost inevitably results in adverse metabolic consequences. Clearly, understanding the underlying mechanisms and rectifying these problems should be seen as the next phase in the 'War on Cancer' – a phase in which high quality endocrinology is essential.

**Adrian Clark**

Editor-in-Chief, *Endocrine Connections*

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Endocrine  
CONNECTIONS





# Your chance to host!

Hosts are needed for two exciting events in the world of endocrinology.

## 30th European Congress of Endocrinology (ECE 2028)

ECE is the leading European conference in endocrinology, presenting renowned speakers from across the breadth of our field. Its reputation for excellence attracts delegates from around the globe.

We are now accepting bid proposals from our National Partner Societies to host ECE 2028. This Congress will be planned as a primarily in-person event with some online attendance. Submissions expressing your intention to bid will be assessed by the ESE Congress Committee and shortlisted and ratified by the ESE Executive Committee.

You will find full details at [www.es-e-hormones.org/bid-for-ec-e-2028](http://www.es-e-hormones.org/bid-for-ec-e-2028). Letters of intent should be submitted by 12 January 2024.

## 12th EYES Annual Meeting (EYES 2025)

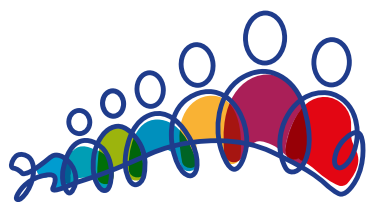
This is your opportunity to host Europe's premier meeting for early career endocrinologists.

The annual ESE Young Endocrinologists and Scientists (EYES) Meeting combines the latest cutting-edge basic, translational, pre-clinical and clinical research, encouraging scientific networking and opportunities for collaboration in a unique, friendly environment.

We invite early career groups in endocrinology, who are linked to an ESE National Partner Society, to apply to host the 12th EYES Annual Meeting in 2025.

You will find further information at [www.es-e-hormones.org/eyes-meeting-bids-2025](http://www.es-e-hormones.org/eyes-meeting-bids-2025). Applications should be submitted by 5 April 2024.

## We look forward to receiving your applications!



### Connecting Endocrinology Across the Life Course

Joint Congress of ESPE and ESE 2025  
Copenhagen, Denmark. 10-13 May 2025

## Save the date ESE/ESPE Joint Congress

'Connecting Endocrinology Across the Life Course' is the theme of the first-ever joint Congress of ESE and the European Society for Paediatric Endocrinology, which will take place on 10-13 May 2025 in Copenhagen, Denmark.

The event will bring together paediatric and adult endocrine specialists from across Europe and beyond. Register your interest at [www.espe-es-e-congress2025.org](http://www.espe-es-e-congress2025.org).

# Würzburg welcomes EYES

The 10th EYES Meeting was a joint conference between EYES (ESE Young Endocrinologists and Scientists) and YARE (Young Active Research in Endocrinology, from the Deutsche Gesellschaft für Endokrinologie).

It took place in Würzburg, Germany, on 8-10 September 2023, attended by 128 early-career clinicians and researchers from 22 countries across Europe and beyond.

Alessandro Brunetti (Italy) received the award for the best oral presentation for 'Bone fragility in well-differentiated gastroenteropancreatic neuroendocrine tumours'. He will give a presentation in the EYES session at ECE 2024. Runner up Nesrine Benanteur (France), who spoke on 'Transcriptome in paraffin samples for the diagnosis and prognosis of pituitary neuroendocrine tumours', will take part in the YARE session during the Deutsche Gesellschaft für Endokrinologie annual conference.



Helsinki, Finland, is the venue for the 11th EYES Annual Meeting on 6-8 September 2024. Find out more about EYES at [www.es-e-hormones.org/eyes](http://www.es-e-hormones.org/eyes).



## Save the date

For more information about any ESE event see [www.es-e-hormones.org](http://www.es-e-hormones.org).

### European Hormone Day

24 April 2024

## ECE 2024

26th European Congress of Endocrinology

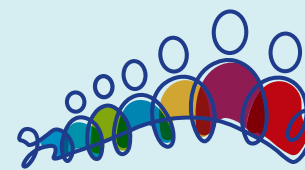
11-14 May 2024

Stockholm, Sweden

### 11th EYES Annual Meeting

6-8 September 2024

Helsinki, Finland



### Connecting Endocrinology Across the Life Course

### Joint Congress of ESPE & ESE 2025

10-13 May 2025

Copenhagen, Denmark

## Deadlines

15 December 2023

### EJE Rising Stars 2024

Application deadline

12 January 2024

### ECE 2028 Hosting

Submission of intentions to bid

15 January 2024

### IFCAH Call for Projects 2024

Submission of letters of intent

22 January 2024

### ECE 2024

Abstract submission deadline

28 February 2024

### ESE Awards 2025

Nomination deadline

15 March 2024

### ECE 2024

Grant application deadline

25 March 2024

### ECE 2024

Super Early Bird registration

5 April 2024

### 12th EYES Annual Meeting

Applications to host

22 April 2024

### ECE 2024

Early Bird registration