Yearbook of Paediatric Endocrinology 2025

Editors
Ken Ong
Christa Flück

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Paediatric Endocrinology 2025

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Preface

Another year has passed, and with it, exciting scientific developments in pediatric endocrinology and diabetology. We had an early glimpse of the latest literature at three oral sessions during the inaugural combined ESPE/ICE meeting in Copenhagen, Denmark—an event that proved to be a resounding success.

Now, we are pleased to present the *Yearbook 2025*, comprising 15 topic-based chapters, each curated by experts in their respective fields. The number of publications continues to grow rapidly. In basic science, single-cell sequencing and ex vivo/in vitro methods took center stage, while novel bioinformatic tools allowed for deeper insights into the genetic landscape of health and disease. Translational studies increasingly blend fundamental and clinical approaches to explore disease mechanisms. Unsurprisingly, machine learning has made a strong entrance into our field, offering both exciting opportunities—and perhaps a few challenges. Most notably, we are witnessing the arrival of a whole new spectrum of medications in the pediatric space, with promising potential to transform outcomes for children and adolescents affected by both rare and common endocrine conditions.

We are deeply grateful to the Chapter Editors, whose dedication to reviewing this year's literature and providing critical commentary has once again made this yearbook possible. Their insights on the impact, limitations, and knowledge gaps in recent research are invaluable. Like last year, members of The Young ESPE (YES) group have also contributed to each chapter, and we thank these highly motivated early-career professionals for their involvement. Their fresh perspectives are a clear testament to the bright future ahead for our field.

We hope you enjoy reading the *Yearbook 2025* and find inspiration and knowledge within its pages.

Warmest regards,

Ken K. Ong and Christa E. Flück

1. Pituitary and Neuroendocrinology

Sare Betul Kaygusuz[1,2], Carles Gaston-Massuet[3]

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Introduction

This year research on pituitary and neuroendocrinology has been extremely rich with outstanding contributions to the field. The number of novel mechanisms and the identification of novel disease-causing genes have increased. Our selection has not been easy, and it only reflects a portion of all the excellent new findings both in basic and translational research. Highlights of this chapter include novel mechanisms that identify that pituitary gonadotrophs (LH/FSH) have dual embryonic origine with most postnatal LH and FSH arising from postnatal Sox2+ve pituitary resident stem cells rather than embryonic stem cells. Another novel mechanism identifies FGF1 expressed from corticotropes cells acting in a paracrine fashion to impact pituitary differentiation and gland architecture. Novel genes important in pituitary disease such as a gene encoding fatty acid synthase (FASN) involved in a complex multisystem disorder including hypopituitarism and hypoparathyroidism or *Nxn*, a redox-sensitive oxidoreductase, had previously been linked to broader developmental syndromes, such as Robinow syndrome. New treatments and hopes include a successful human study using intranasal administration of kisspeptin demonstrating that it can rapidly and effectively stimulate the release of gonadotropins (LH and FSH) in humans, providing evidence as potential therapeutic avenue that could be applied to the management of reproductive disorders. Overall, the research presented in this chapter exemplifies the fast-advancing field and extraordinary basic genetic research is providing translational outputs to the benefit of the patients.

New Mechanisms

1.1. Gonadotrophs have a dual origin, with most derived from early postnatal pituitary stem cells

D. Sheridan, P. Chakravarty, G. Golan, Y. Shiakola, J. Olsen, E. Burnett, C. Galichet, T. Fiordelisio, P. Mollard, P. Melamed, R. Lovell-Badge, K. Rizzoti
Nat Commun 16, 4280 (2025).
PMID: 40399281

Brief Summary: This experimental study presents compelling evidence that murine postnatal gonadotrophs have a dual origin. Traditionally thought to arise from embryonic stem cells, this research now demonstrates that the majority of adult gonadotrophs derive from postnatal $Sox2^+$ pituitary stem cells, particularly during early life and up to puberty. Surprisingly, this second wave of differentiation occurs independently of gonadal hormones and GnRH signalling, suggesting an intrinsic, stem cell-driven expansion mechanism to establish reproductive capacity.

This study used sophisticated cell lineage tracing combined with single cell transcriptomic analyses to show that pituitary gonadotrophs (that produce LH and FSH) are derived mainly postnatally from Sox2+ve Sox9+ve pituitary resident stem cells. The authors generate a novel genetic lineage tracing murine line, *Sox2rtTA* (activated with doxycycline, that avoids tamoxifen effects on hypothalamic-pituitary-gonadal axis), allowing

precise temporal labelling of $Sox2^{+}$ stem cells (*Sox2rtTA;RosaYFP*) during postnatal time windows. Cell lineage tracing shows that some gonadotrophs are produced embryonically form embryonic Sox2+ve stem cells but these represent only a minority of the adult LH-FSH adult gonadotrophs as the majority are produced postnatally during a winddown time of mini-puberty. Importantly, the authors show that gonadotroph production is independent of GnRH or the feedback loops from gonads since ablation of these signals still results in gonadotroph differentiation. Single-cell transcriptomics and imaging: UMAP and pseudotime revealed a clear trajectory from Sox2 stem cells toward gonadotroph identity. Hence, this second wave of differentiation occurs independently of gonadal hormones and GnRH signalling, suggesting yet unknown intrinsic signal that triggers stem cell-driven expansion mechanism to establish reproductive capacity.

The findings are important in pituitary research field in several aspects as it identifies 2 temporally distinct populations of cell fate regulation. This may underlie functional or regulatory differences among gonadotroph subtypes (embryonic versus postnatal origin), which are yet unknown. Given that most gonadotrophs form postnatally, this window could be a vulnerability point. The authors propose that disorders like congenital hypogonadotropic hypogonadism (CHH) might distinctly affect embryonic vs. postnatal lineages, a hypothesis that needs to be tested in future studies. Importantly, since the authors show that the stem cell that will give rise to the majority of gonadotrophs arise independently of GnRH/gonadal signals, there's the exciting prospect of harnessing endogenous signals to restore gonadotroph function, for example, in hypogonadism or pituitary injury.

Although GnRH/gonadal independence is shown, what upstream signals drive stem cell differentiation is not known. This study leaves open the mechanistic question of niche cues or systemic factors involved in triggering this second gonadotroph wave. Moreover, confirming whether human pituitary has a similar dual-origin architecture is essential, especially for designing regenerative strategies.

1.2. Paracrine FGF1 signaling directs pituitary architecture and size

K. Khetchoumian, K. Sochodolsky, C. Lafont, A. Gouhier, A. Bemmo, Y. Kherdjemil, M. Kmita, P. Le Tissier, P. Mollard, H. Christian, J. Drouin

Proc Natl Acad Sci USA 121(40) (2024) e241026912.
PMID: 39320918

Brief Summary: The architecture and function of the anterior pituitary rely on precise cell-cell communication within interdigitated hormone-secreting networks. However, the specific signals orchestrating these interactions remained unknown. This experimental study identifies that corticotrope-derived factors, particularly the secreted FGF1, play a pivotal paracrine function in sustaining pituitary structure and growth.

This study from Drouin's laboratory uses elegant murine genetics tools combined with single-cell transcriptomic analyses and functional validation in vitro and in vivo to identify a novel role of secreted FGF1 from corticotropes. The authors identify that mouse knock-out of Tpit (a corticotrope-specific transcription factor) leads to marked pituitary hypoplasia and diminished somatotrope cell numbers causing systemic growth defect. Single-cell RNA-seq revealed that FGF1 expression in corticotropes is Tpit-dependent and this is further demonstrated using ATAC and CHIP-seq. Moreover, loss of *Fgf1* recapitulated the phenotypes observed in Tpit deficiency. Fgf1 knockout mice exhibit reduced pituitary size, somatotrope hypoplasia, disrupted cell polarity, and stunted growth, mirroring Tpit-KO phenotypes. Together, these results compellingly position FGF1 as a corticotrope-secreted paracrine morphogen essential for proper pituitary architecture and growth.

As with all great papers, there are some open questions for this work. While loss of FGF1 mirrors loss of Tpit, the reverse approach (rescue experiments by exogenous FGF1 in Tpit-KO) would greatly strengthen causality. Although mouse data are compelling, translational relevance to human pituitary development or disease will require further experiments. Interestingly mutations in Fgf8 have been identified in patients with congenital hypopituitarism's (CH) indicating the role of this pathway in pituitary hormone deficiencies in humans. Hence, further investigation to identify if mutations in FGF1 or its receptors are cause of CH in humans are warranted. Overall, this study sets the stage for a richer understanding of paracrine-driven organogenesis in complex endocrine systems.

1.3. Nucleoredoxin regulates WNT signaling during pituitary stem cell differentiation

M.L. Brinkmeier, L.Y.M. Cheung, S.P. O'Connell, D.K. Gutierrez, E.C. Rhoads, S.A. Camper, S.W. Davis
Hum Mol Genet 34(10) (2025) 870-881.
PMID: 40044116

Brief Summary: This experimental study sheds new light on the critical role of *Nucleoredoxin* (Nxn) in orchestrating WNT signalling during pituitary stem cell differentiation. Nxn, a redox-sensitive oxidoreductase, had previously been linked to broader developmental syndromes, such as Robinow syndrome.

The authors used RNAscope to show strong *Nxn* expression in Rathke's pouch, infundibulum, ventral diencephalon, and co-expression with $Sox2^{+}$ stem/progenitor cell populations, positioning Nxn at critical sites for pituitary lineage decisions. Moreover, phenotypic analyses of $Nxn^{-/-}$ embryos demonstrated dysmorphic features such as cleft palate and pituitary abnormalities from e11.5 onward, basisphenoid bone ossification defects. These phenotypes are reminiscent of human Robinow syndrome. The authors used single-cell mRNA-seq at e14.5; this uncovered reduced non-canonical WNT5A signalling and a shift in pseudotime trajectories. Stem/progenitor cells accumulated, while differentiated thyrotropes and other lineages were depleted. The data suggests a model where Nxn regulates non-canonical WNT singalling, to enable stem-to-lineage transitions in the pituitary, likely through redox modulation of WNT components such as DVL.

This is work places NXN as a pivotal factor in enabling stem cells to exit an undifferentiated state, implicating redox-regulated WNT cues in early pituitary cell fate decisions. Given that human *NXN* mutations cause recessive Robinow syndrome (characterized by skeletal and craniofacial malformations), these findings suggest endocrine evaluation is warranted for patients, particularly regarding pituitary structure and hormone status. It will be valuable to confirm these mouse findings in humans, by examining anterior pituitary function in Robinow patients with *NXN* mutations.

Overall, this is a compelling, methodologically rigorous study that addresses fundamental questions in pituitary development while offering translational value for human disorders. It opens avenues for deeper investigation into redox regulation of WNT and for potential endocrine evaluation in related congenital syndromes such as Robinow syndrome.

Novel Genes

1.4. A complex multisystem disorder including hypopituitarism and hypoparathyroidism, associated with mutation in the gene encoding fatty acid synthase (FASN)

L.C. Gregory, S. Krywawych, S. Rahman, C.F. Lagos, S. Eaton, M.T. Dattani
Metabolism 168 (2025) 156256.

Brief Summary: This case report describes endocrine and neurological dysfunction in a male patient with a de novo mutation in FASN (p.Ala2132Val). He displayed hypopituitarism, hypoparathyroidism, sensorineural deafness, retinal dystrophy, developmental delay, and growth failure. This work suggests that perturbing the fatty acid synthase enzyme can disrupt hypothalamo pituitary development and endocrine homeostasis.

This paper from Dattani's laboratory introduces a human syndrome linking FASN-dependent lipogenesis to pituitary and endocrine system development. This work elegantly bridges metabolism, development, and endocrine dysfunction, positioning FASN as a novel CH-causing gene. They used clinical phenotyping and genetics to present a correlation between a novel *FASN* variant (FASN p.Ala2132Val) with robust exclusion of many other CH-causing genes in humans. Moreover, they use biochemical assays in fibroblast to demonstrate that *FASN* p.Ala2132Val markedly reduces the novo lipogenesis to confirm FASN pathogenic impact. They show that *FASN* is expressed in the HP-axes during human development. The report aligns with rodent studies showing that de novo lipogenesis in neural stem and progenitor cells (NSPCs) is essential for proliferation and

brain development. Here, reduced FASN activity disrupted human hypothalamo pituitary development, as evidenced by persistent prepuberty, panhypopituitarism, and lack of growth response. *FASN* expression in parathyroids and retina neatly explains the co-occurrence of hypoparathyroidism and retinal dystrophy. This supports the notion that lipogenesis is a cross-tissue developmental requirement for normal physiology leading to multi-organ failure.

This study has broader clinical relevance and opens to further research to test if patients with *FASN* variants have similar presentation to that reported here. Moreover, screening in congenital hypopituitarism cohorts should clarify the prevalence of *FASN* variants in CH. This study seeds new inquiries into metabolic regulation of endocrine ontogeny and underscores the need to consider metabolic defects in unexplained hypopituitarism. It is poised to reshape our understanding of congenital endocrine disorders and opens avenues for targeted diagnostic and therapeutic strategies.

1.5. Long noncoding RNAs expressed in mouse pituitary development and mature hormone-producing cell

M.L. Brinkmeier, A.S. George, L.Y.M. Cheung, R.E. Mills, P. Melamed, S.A. Camper
Endocrinology 165(12) (2024).
PMID: 39487735

Brief Summary: This experimental study presents a valuable resource of transcriptomic analyses to identify cis-acting long noncoding (lnc) RNAs during murine pituitary development.

This paper from Camper's laboratory presents an excellent resource of lncRNA expression in the developing and adult mouse pituitary, focusing on 3 major hormone producing lineages: thyrotropes, gonadotropes, and somatotropes. Through RNA seq analysis of pituitaries at embryonic days (E) 12.5 and E14.5, they identified over 200 embryonic lncRNA transcripts. Moreover, the authors use fluorescent tagging and fluorescent activated sorting (FACs) to isolate the specific cell types, detecting hundreds more lineage-specific lncRNAs. The authors find that a subset of these lncRNAs were genomically positioned immediately adjacent to genes encoding pituitary hormones or important transcription factors required for pituitary development. The authors hypothesise that these **lncRNAs** may have **cis-regulatory potential**. Two of these lncRNAs displayed correlated expression – in transgenic mouse models – with their nearby protein-coding targets.

This work offers a detailed atlas of developmentally and cell-type-specific lncRNAs within the pituitary. The dataset is available and hence represents a unique resource to study candidate lncRNAs. The spatial proximity of many lncRNAs to hormone genes (e.g., Cga, Foxl2) suggests they may regulate nearby gene expression by altering chromatin states, modulating transcription, or forming RNA-DNA interactions. While intriguing, these roles remain to be experimentally confirmed.

1.6. Developmental exposures to common environmental pollutants result in long-term reprogramming of hypothalamic-pituitary axis in mice

J.P. Mogus, M. Marin, O. Arowolo, V. Salemme, A. Suvorov
Environ Pollut 361 (2024) 124890.
PMID: 39236844

Brief Summary: This experimental study identified long-term changes in gene expression in the hypothalamic-pituitary (HP)-axis in murine models exposed to relevant doses of endocrine-disrupting chemicals (EDCs) during pregnancy and perinatal periods.

The authors used 3 common EDCs: bisphenol-S (BPS), 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47) and 3,3′,5,5′-tetrabromobisphenol A (TBBPA), at relevant doses, to assess long term effect on the brain HP-axis gene expression, using mRNA-seq followed by qPCR. These EDCs caused specific long term gene expression

changes in the CD-1 mouse HP-axis, exposed during pregnancy and lactation. Exposure timing focused on pregnancy from day 8 through weaning, which captures critical developmental windows for neuroendocrine brain regions. The authors use multi-tiered molecular analysis, RNA seq and RT qPCR for pituitaries and hypothalamus that allows both broad screening and focused gene validation. The authors use (0.2 mg/ml) concentration of EDCs which approximates environmentally relevant exposures, enhancing translational significance. All 3 chemicals down regulated pituitary genes tied to endocrine function (Gh, LHb, CRH), with BPS and BDE 47 showing strong overlap in affected pathways. Across the board, there was reduced expression in immune-related genes and GPCR-mediated signalling cascades, indicating altered hormone responsiveness and immune surveillance at the pituitary level. In the hypothalamus the authors report down regulation of important hypothalamic function genes such as *Esr1, Crh, Ghrh*, among others.

Future studies are needed to functionally characterise these transcriptional changes and their physiological impact in isolation or in combination. The authors studied only males; future studies should use a non-sex biased approach to understand the effect of these EDCs in females. The study offers compelling evidence that low level developmental exposure to ubiquitous EDCs can reprogram central endocrine regulators. These findings set a new paradigm in understanding how environmental contaminants shape lifelong health outcomes.

1.7. Endocrinological features and epileptic encephalopathy in COX deficiency due to SCO1 mutations: case series and review of literature

A. Barbato, G. Gori, M. Sacchini, F. Pochiero, S. Bargiacchi, G. Traficante, V. Palazzo, L. Tiberi, C. Bianchini, D. Mei, E. Parrini, T. Pisano, E. Procopio, R. Guerrini, A. Peron, S. Stagi

Endocr Connect 13(10) (2024).
PMID: 39214134

Brief Summary: The retrospective case series describes 3 children with pathogenic *SCO1* mutations leading to early-onset encephalopathy and progressive panhypopituitarism.

SCO1 is a nuclear gene that is essential for the proper assembly of mitochondrial complex IV (cytochrome c oxidase, COX), which plays a critical role in oxidative phosphorylation. Biallelic *SCO1* mutations have been associated with fatal mitochondrial encephalopathy, often with metabolic acidosis and liver failure. To date, only 6 patients with *SCO1* mutations have been reported, 5 of whom died at an early age [1-5].

Here, growth hormone deficiency and central hypothyroidism was observed in all 3 patients. In addition, 2 showed adrenal insufficiency and hypogonadotropic hypogonadism. Notably, hepatic dysfunction was absent, and cardiac involvement was mild or not observed. The authors hypothesise that this relatively milder phenotype and extended survival may be due to the presence of missense variants in *SCO1*, as opposed to previously reported truncating variants. Therefore, the development of hypopituitarism may have been only observable due to the longer survival afforded by their milder mitochondrial phenotype.

In summary, this article describes the first reported association between panhypopituitarism and *SCO1*-related COX deficiency, thereby expanding the phenotypic spectrum of *SCO1*-associated mitochondrial disease. Furthermore, the study highlights the necessity for regular endocrine surveillance in individuals with *SCO1* variants in order to monitor the progression of pituitary dysfunction.

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1.8. Gonadotropin therapy for mini-puberty induction in male infants with hypogonadotropic hypogonadism

S. Rhys-Evans, F. d'Aniello, E.C. Alexander, I.F. Dinah, S. Heger, A. Nordenstrom, J. Rohayem, S.R. Howard
J Clin Endocrinol Metab 110(4) (2025) e921-e931.
PMID: 39673783

Brief Summary: This systematic review and meta-analysis examined the induction of mini-puberty using exogenous gonadotropins in male infants with congenital hypogonadotropic hypogonadism (CHH). The evidence supports the efficacy of this clinical therapeutic approach to induce mini puberty.

Mini-puberty, the transient activation of the hypothalamic-pituitary-gonadal (HPG) axis during the first few months of life, plays a critical role in male genital development, Sertoli and Leydig cell maturation, and potential future fertility. In CHH, this window is missed, with consequences including micropenis, undescended testes, and impaired testicular function.

This multicenter systematic meta-analyses review suggests that combined recombinant human LH and FSH therapy mimics the physiological patterns of mini-puberty. The findings indicate improvements in genital development (notably penile length and testicular descent) and biochemical responses: elevated testosterone, AMH, and inhibin B, suggesting functional activation of Leydig and Sertoli cells.

Strengths of the study are its well-structured design and use of validated clinical and biochemical endpoints. Moreover, the inclusion of longitudinal follow-up enhances the relevance of the data to future fertility considerations.

This study supports a shift towards earlier, targeted intervention during infancy, potentially improving future fertility outcomes by rescuing early testicular development. While the sample size reflects the rarity of CHH, the biochemical and anatomical responses were consistent and clinically meaningful. This work raises important considerations: What are the long-term reproductive outcomes of early gonadotropin exposure? Should all boys with CHH routinely offer this therapy? And how can we standardize early diagnosis to allow timely initiation of treatment? Future studies will provide with important clinical data supporting the treatment for CHH during mini-puberty.

1.9. Cushing syndrome in paediatric population: who and how to screen

L. Chioma, G. Patti, M. Cappa, M. Maghnie
J Endocrinol Invest 48(Suppl 1) (2025) 7-19.
PMID: 39347909

Brief Summary: Cushing's syndrome (CS) is characterized by prolonged and excessive exposure to glucocorticoids, resulting in significant morbidity and mortality. The authors reviewed literature published between 1970 to 2023, and summarize current screening strategies and updates in biochemical testing and imaging. They propose a pragmatic, stepwise diagnostic approach.

Although rare, paediatric CS is associated with significant morbidity. Early and accurate recognition is essential to reduce the complications. The classification of Cushing's syndrome (CS) is determined by its etiology, which can be categorised: pituitary (Cushing's disease, CD), ectopic ACTH secretion, or adrenal origin. It is imperative and sometimes challenging to differentiate between non-neoplastic hypercortisolism (NNH), often caused by psychiatric conditions, obesity, or extreme physical stress, as initial screening tests may yield false positives [1, 2].

The authors endorse current consensus guidelines recommending late-night salivary cortisol (LNSC), 24-hour urinary free cortisol (UFC), and 1-mg dexamethasone suppression test (DST) as initial tools [2]. The authors highlight the limitations and advantages of each: UFC requires multiple samples due to high variability; DST may yield false positives due to altered dexamethasone metabolism; LNSC is advantageous for being non-invasive. Measurement of dexamethasone levels is recommended in children to reduce false positives. The use

of LC-MS/MS assays, which allow the quantification of cortisol and cortisone, is proposed to enhance the identification of endogenous cortisol production, and to reduce the occurrence of false-positive results.

The authors maintain that MRI remains the standard imaging modality for CD, with spoiled gradient-recalled acquisition in the steady state MRI enhancing adenoma detection being a key advancement. Functional imaging techniques with new molecules (e.g., 68Ga-DOTATATE PET/CT for small tumours, 11C-metomidate PET/CT for adrenal lesions) offer promise but require further validation. In many cases, a non-invasive approach using 3 to 4 biochemical and imaging modalities may obviate the need for bilateral inferior petrosal sinus sampling (BIPSS).

In conclusion, early suspicion, and proper use of LNSC, UFC and DST improves diagnostic accuracy. A non-invasive, stepwise approach may reduce reliance on BIPSS in selected cases.

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1.10. Phenotype and genotype of 23 patients with hypopituitarism and pathogenic GLI2 variants

K. Aouchiche, C. Charmensat, P. Morgane, C. Teinturier, P. Bretones, A. Brac de la Perriere, V. Layet, N. Bouhours-Nouet, M.C. Vantyghem, E. Haine, M.L. Nunes-Sanchez, O. Camard, S. Baron, F. Castinetti, A. Barlier, T. Brue, R. Reynaud, A. Saveanu

N. Eur J Endocrinol 192(2) (2025) 110-118.

PMID: 39938560

Brief Summary: *GLI2* has been identified as the most prevalent genetic cause of syndromic hypopituitarism. This multicenter retrospective study used data from the GENHYPOPIT network on 23 patients with congenital hypopituitarism carrying pathogenic or likely pathogenic *GLI2* variants in order to identify genotype–phenotype correlations.

Congenital hypopituitarism (CH) is a heterogeneous and incompletely understood condition, classically divided into two subtypes: non-syndromic CH, characterized by isolated anterior pituitary hormone deficiencies, and syndromic CH, which is characterised by the association of hormonal deficits with structural brain or extracerebral anomalies. GLI2 is a key transcription factor in the Hedgehog pathway, and its role in pituitary development has been recognized with several reports have already associated CH with GLI2 variants [1, 2, 3].

This study identified 17 pathogenic or likely pathogenic *GLI2* variants, affecting 23 patients (17 index cases and 6 affected relatives). Of those, 91% had hypopituitarism; 65% with combined pituitary hormone deficiency and 22% with isolated growth hormone deficiency. The authors highlight the incomplete penetrance (67%) and variable expressivity of *GLI2* variants. Notably, some patients developed late-onset ACTH deficiency, underscoring the need for lifelong endocrine monitoring. MRI abnormalities, particularly PSIS, were observed in 84% of cases. A range of associated features were identified, including neurocognitive impairment (38%), postaxial polydactyly (27%), Kallmann syndrome, cardiac defects, and renal/urogenital anomalies.

This study supports the need for a systematic malformation workup, including renal and cardiac imaging in affected individuals and also potentially evolving corticotrope deficiency. The study also broadens the phenotypic spectrum of *GLI2* to encompass Kallmann syndrome.

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1.11. Intranasal kisspeptin administration rapidly stimulates gonadotropin release in humans

E.G. Mills, M.S.B. Silva, V. Delli, L. Decoster, G. Ternier, J. Tsoutsouki, L. Thurston, M. Phylactou, B. Patel, L. Yang, S.A. Clarke, M. Young, E.C. Alexander, S. Nyunt, A.C. Yeung, M. Choudhury, A. Newman, P. Bech, A. Abbara, M. Swedrowska, B. Forbes, V. Prevot, K. Chachlaki, P. Giacobini, A.N. Comninos, W.S. Dhillo

EBioMedicine 115 (2025) 105689.

PMID: 40215751

Brief Summary: This study shows that intranasal administration of kisspeptin rapidly and effectively stimulates the release of gonadotropins (LH and FSH) in humans. The findings provide evidence for the potential therapeutic use of kisspeptin in the management of reproductive disorders.

The authors examined a novel, non-invasive delivery route for kisspeptin in humans and rodents. Kisspeptin is neuropeptide critical for the regulation of the hypothalamic-pituitary-gonadal (HPG) axis. By demonstrating that intranasal administration of kisspeptin (12.8 nmol/kg) can rapidly and effectively stimulate the release of gonadotropins (LH and FSH) in humans, the authors provide clinical evidence for a new therapeutic avenue that may change the management of reproductive disorders.

The authors conducted human trial to directly assess the physiological impact of kisspeptin delivered via the nasal mucosa. Hormone profiles were measured after intranasal administration both in healthy and patients with reproductive disorders. The observed rapid rise in circulating gonadotropins highlights both the bioavailability and biological potency of intranasal kisspeptin. This route of administration could circumvent the need for injectable therapies, offering increased patient compliance and broader accessibility.

The findings hold promise for clinical conditions such as hypogonadotropic hypogonadism, delayed puberty, and potentially infertility due to hypothalamic dysfunction. The fast-acting nature of the response suggests that kisspeptin could also be used diagnostically, in a manner analogous to GnRH stimulation testing, to assess pituitary responsiveness in real time. The authors go one step further and use rodents to administer kisspeptin-54 fluorescently tagged and demonstrate the same hormonal response that in humans. The rodent studies allow them to show that tagged-kisspeptin binds to GnRH neurons from the olfactory bulbs (OB) triggering physiological response. The authors show that OB neurons express kisspeptin receptor hence postulating a mode of action of nasal kisspeptin treatment by acting on the OB GnRH neurons.

Unlike exogenous gonadotropin injections, kisspeptin acts upstream of LH/FSH, triggering a more physiologically regulated release of endogenous hormones. This could reduce the risk of ovarian hyperstimulation syndrome (OHSS), a serious complication of fertility treatments.

There are questions that warrant further exploration. For example, the duration of the gonadotropin response, the effects of repeated dosing, interindividual variability, and the efficacy in populations with reproductive pathology remain to be fully characterized. Additionally, while the intranasal route appears effective, future studies should assess its pharmacokinetics and optimal dosing regimens across sexes, age groups, and clinical conditions.

1.12. Semaglutide as a promising treatment for hypothalamic obesity: a six-month case series on four females with craniopharyngioma

E. Gjersdal, L.B. Larsen, K.S. Ettrup, P. Vestergaard, E.H. Nielsen, J.S. Karmisholt, H.L. Muller, J. Dal

Pituitary 27(5) (2024) 723-730.

PMID: 39088138

Brief Summary: Patients with hypothalamic pathology often develop hypothalamic obesity (HO), a challenging condition with limited available therapeutic options. This case series reports the effects of semaglutide treatment in HO.

HO is characterized by abnormal weight gain due to hypothalamic pathology, and presents with not only obesity, but also with multiple endocrine alterations, as well as an increased risk of cardiometabolic disorders [11]. HO

develops due to dysfunction of the hypothalamus, which may result from either genetic or acquired diseases, or from treatment. Suprasellar tumours are the most common acquired cause of HO [12]. Cases of HO are challenging and have limited treatment options. GLP-1 receptor agonists as a treatment for HO does not appear to depend on a functional leptin–POMC–MC4R pathway, a factor that may prove advantageous in the management of HO [13]. Studies conducted on the effects of exenatide and liraglutide, yet those findings are inconclusive with regard to the consistent weight loss [14-17]. By contrast, semaglutide has been reported to have a more potent effect [18].

This study examined the effect of semaglutide in 4 female patients with HO. Their initial BMI values ranged from 36 to 55.5 kg/m^2. Following intervention, a reduction in BMI was observed in all cases, with an average decrease of 7.9 BMI (range: 6.7 to 10.1), corresponding to a weight loss of 17.0% (range: 11.3–22.4%). Total body fat and lean mass also decreased. A substantial decrease in body fat was observed in both the trunk (16.4%) and the extremities (upper 21.8%; lower 17.1%). All 4 cases showed improved mobility and physical activity. Unfavorable eating behaviors were reduced after 1 month of treatment, and remained low (emotional eating -41 points, $P = 0.02$, uncontrolled eating -23 points, $P = 0.11$). After 6 months, reductions were observed in HbA1c and total cholesterol.

This study demonstrates that semaglutide is an effective and secure treatment option for HO, with the ability to modify eating behavior, reduce weight, and improve glucose and lipid metabolism.

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2. Antenatal and Neonatal Endocrinology

Cheri Deal[1], Hanife Gül Balki[2]

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Introduction

This section of the *Year in Review* continues to see important advances in our understanding the etiology of endocrinopathies and of pre- and post-natal growth disorders, including new gene variants, genomic associations, epigenetics and transcriptomics. New therapies continue to receive attention for rare diseases or conditions diagnosed in the fetus or infant, and more data is accruing on the impact of maternal medications during pregnancy – such as the GLP-1 agonists and metformin - on the fetus and newborn. Many of these excellent studies involve international collaborations, underlining the efficiency, progress, patient benefits and importance of global scientific efforts. As always, the choice was difficult.

Sex Chromosome Aneuploidies

2.1. The transcriptomic landscape of monosomy X (45,X) during early human fetal and placental development

Jenifer P. Suntharalingham, Ignacio del Valle, Federica Buonocore, Sinead M. McGlacken-Byrne, Tony Brooks, Olumide K. Ogunbiyi, Danielle Liptrot, Nathan Dunton, Gaganjit K. Madhan, Kate Metcalfe, Lydia Nel, Abigail R. Marshall, Miho Ishida, Neil J. Sebire, Gudrun E. Moore, Berta Crespo, Nita Solanky, Gerard S. Conway, John C. Achermann

Commun Biol. 2025 Feb 16;8(1):249.
doi: 10.1038/s42003-025-07699-4

Brief Summary: These investigators sought to understand why complete or partial loss of the second X chromosome not only explains the high incidence of fetal demise in monosomy X Turner Syndrome but also results in a panoply of clinical signs and symptoms beginning in prenatal life and extending throughout the lifespan. Previous genotype-phenotype studies have shed some light[1] but this study focused on bulk RNA-seq using human monosomy X fetal samples (placenta, liver, kidney, pancreas, skin and mixed group of brain, heart, lung and spleen) between 11 and 15 weeks post-conception compared to tissue- and age-matched 46,XX and 46, XY controls.

Major findings of this first multi-tissue, detailed transcriptome analysis include: 1) As expected for haploinsufficiency of the pseudoautosomal region (PAR) genes, lower expression was found in many, but not all, PAR1 and PAR2 genes and not entirely because of tissue-specific gene expression, suggesting possible compensatory mechanisms; 2) Some non-PAR genes escaping X-chromosome inactivation were also decreased, that are known to play a role in transcription, translation and histone methylation status - all important for fundamental developmental processes;3) Genes showing decreased expression in all tissues included some enrichment for connective tissue pathways linked to aneurysms and connective tissue disorders; 4) One gene upregulated in multiple tissues is a long non-coding RNA. These types of RNA are involved in gene and post-transcriptional regulation, chromatin modification, and several other fundamental cellular mechanisms; 5) The placenta-specific PAR1 gene *CSF2RA* (encoding a granulocyte-macrophage colony-stimulating factor receptor subunit) showed decreased expression (as were other transcripts in immune and inflammatory pathways), with immunohistochemistry for this gene showing non-specific placental inflammatory changes. This suggests that dysregulation of immune/inflammatory pathways may contribute to placental dysfunction – and if so, to early fetal demise.

The strength of this study lies in its original approach and in the wealth of testable hypotheses that it generated. It is further supported by the known rare variants in some of the same genes found in this study which have been

implicated in phenotypes such as Kabuki Syndrome (horseshoe kidney, hearing loss), Marfan's syndrome (associated with thoracic aortic aneurysms), dyslipidemia and hypertension.

Reference

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2.2. Ultra-rare monogenic disorders frequently detected among sex chromosome aneuploidy patients with atypical findings

Kiana Magee, William McGonigle, Rena Pressman, Willa Thorson, Deborah Barbouth, Nicholas A. Borja

J Hum Genet. 2025 Mar 70(3):177-179.
doi: 10.1038/s10038-024-01312-y

Brief summary: The question asked by these investigators is how often patients with identified sex chromosome aneuploidies (SCA) need to have further genetic workups. While severe, atypical phenotypes are always a red flag, the increasing numbers of patients coming to prenatal diagnosis has lead to increased understanding of phenotypic variability, and physicians may be less likely to refer. This retrospective study evaluated 54 pediatric patients over 9 years with cytogenetically diagnosed SCA. Twelve (22%) of these were identified as having discordant or severe phenotypes, and 11 patients went for further testing. Five of these 11 patients (41.7 %) were found to have a second genetic syndrome, based on next-generation sequencing and array comparative genomic hybridization. In all of these 5, there were phenotypic similarities in the two diagnoses, but with the second diagnosis explaining the unusual findings for the specific SCA. These children included: 1) Monosomy Turner Syndrome, found to have situs inversus totalis, with compound heterozygosity for 2 pathogenic variants in *DNAH5* (associated with primary ciliary dyskinesia 3 +/- situs inversus; 2) Turner Syndrome with an isodicentric Xp11.22q28 with cleft lip and palate, aural atresia and anterior displacement of the anus, with a likely homozygous pathogenic variant in *TXNL4A*causing Burn-McKeown Syndrome; 3) Klinefelter 47,XXY with developmental delay, seizures, central sleep apnea, and mitral insufficiency, with a 1.28 Mb deletion of 2p23.3 encompassing the gene associated with Tatton-Brown-Rahman Syndrome (*DNMT3A*); 4) Triple X Syndrome, with an unusually severe neurologic phenotype including epilepsy, with a pathogenic variant in a SET-domain binding protein,*SETD1B* explaining her neurodevelopmental disorder; 5) Triple X Syndrome with macrocephaly and overgrowth, also with a SET-related disorder.

A key message is that we can no longer assume that uncomplicated SCA fully explains atypical phenotypes. Inordinately long referral time to genetic specialists despite the presence of atypical phenotypes might have been avoided for these 5 patients, leading to better care. The authors would like to see atypical findings in any patient with SCA be added to the list of the American College of Medical Genetics Guidelines[1], which already recommends exome or genomic sequencing as first-line testing for pediatric patients with congenital anomalies, intellectual disability and developmental delay. And, of course, a very good history and physical examination must always be done to document all observed findings.

Reference

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2.3. Testosterone effects on short-term physical, hormonal, and neurodevelopmental outcomes (TESTO) in infants with 47,XXY

Shanlee Davis, Susan Howell, Jennifer Janusz, Najiba Lahlou, Regina Reynolds, Talia Thompson, Karli Swenson, Rebecca Wilson, Judith Ross, Philip Zeitler, Nicole Tartaglia

J Clin Endocrinol Metab 2025. Online ahead of print.
doi: 10.1210/clinem/dgaf217

Brief Summary: This randomized, double-blind, placebo controlled cross-over trial from one tertiary care center aimed to assess the safety and efficacy of monthly testosterone in prenatally identified, non-mosaic infants with 47,XXY. Infants with Klinefelter Syndrome undergo a mini-puberty, although measured blood testosterone concentrations are lower than average but usually within the low normal range. How this impacts on their many phenotypic features is unknown; some studies suggest that lower birth weight, mild hypotonia and a passive temperament may be subtle signs. Less than 10% of these infants have micropenis and/or cryptorchidism but most series document smaller penile and testicular size in infancy, but with gonadarche occurring at the expected age range[1]. Non-randomized trials of early testosterone therapy described higher motor, cognitive, language and social skills, but well designed and powered trials have been lacking.

In this study, infants ($n = 71$) aged between 30-90 days were randomized and were given either (group A) 25 mg i.m. testosterone cypionate every 28 d for 3 doses followed by 3 doses of saline i.m. saline, or (group B) 3 doses of saline followed by 3 doses of testosterone. Primary outcomes were the change in percent fat mass SDS from baseline to 12 weeks and the change in the total Alberta Infant Motor Scale (AIMS) during this same period. Secondary and exploratory outcomes included a change in scores from baseline to 12 weeks and 12-24 weeks for other body composition variables, anthropometric measurements, standard scores on a range of other development assessment tools, serum hormone concentrations, and adverse events. Unfortunately, COVID 19 prevented full completion of all the variables in a small group of patients in this study, although only 1 patient was lost to follow-up.

Results attributable to testosterone treatment included lower %FM SDS -0.57 [$p = 0.03$] and greater increases in lean mass of1.5 kg vs 1.2 [$p = 0.001$]. Penile length also increased, as did body length and weight. Expected side effects of testosterone therapy were noted (increased erection frequency, pubic hair, acne) but the treatment was well tolerated with no serious adverse events. As expected, blood concentrations of LH, FSH, and inhibin B were suppressed on treatment. There were no significant differences in all the observed short term motor, cognitive or language scores. The investigators concluded that routine testosterone treatment in infants with 47,XXY is not supported based on their neurodevelopmental data, but it will be important to continue with longer term follow up particularly on neurodevelopment, behavior and testicular function.

Reference

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Rare Syndromes

2.4 Clinical delineation and genotype–phenotype correlation in 104 children with Kabuki syndrome: a single-center, cross-sectional and follow-up study in China

Yirou Wang, Feihan Hu, Xueqiong Xu, Jun Tan, Tingting Yu, Niu Li, Qian Li, Yao Chen, Guoying Chang, Xiuqi Ma, Ding Yu, Xiumin Wang

Eur J Pediatr 2025 Mar 27;184(4):271.
doi: 10.1007/s00431-025-06103-x

Brief Summary: This is an important longitudinal study of 104 Chinese patients with Kabuki syndrome (KS, OMIM #147920 and #300867), and the largest to date. It provides the first growth curves for this rare syndrome based on WHO 2007 standards, as well as detailed phenotypic data.

In order to be included, all patients had pathogenic or likely pathogenic variants in *KMT2D* or *KDM6A* (both encode histone demethylases) on whole genome sequencing followed by Sanger sequencing. Facial recognition software (Face2Gene) correctly identified 85 patients of the 99 patients providing photographs, with some concern for photograph quality for those not confirmed.

In the 89 patients with *KMT2D* mutations (KS1), 78 variants were scattered throughout the gene but 29.2% were within exon 39. In the 15 KS2 patients with *KDM6A* mutations, 14 different variants were reported.

Predicted adult height data (excluding GH deficient/treated patients): KS1-Male -1.43 SD, KS1-Female -1.86 SD,KS2-Male -1.26 SD, KS2-Female -0.98 SD. Growth kinetics suggested that, in addition to a 25-30% incidence of fetal growth restriction and stature < -2 SD in ~30% of patients, they lack a pubertal growth spurt. While all patients with KS1 had intellectual disabilities, some with KS2 mutations had intelligence in the normal range; a very high proportion (60-80%) had dysarthria, and renal, cardiac and cleft palate are among the notable malformations.

This paper should improve our diagnostic suspicion for KS and prompt consideration of facial dysmorphology software to make a diagnosis, pending genetic testing.

2.5. Trametinib as a targeted treatment in cardiac and lymphatic presentations of Noonan syndrome

Isabel De Brouchoven, Juan Lorand, Léon Bofferding, Arthur Sorlin, An Van Damme, Olivier Danhaive
Front. Pediatr. 2025 Feb;13:1475143.
doi: 10.3389/fped.2025.1475143

Brief Summary: This case report describes acritically ill neonatal patient withNoonan Syndrome (NS)[1],who successfully received a course of the monoclonal selective allosteric MEK inhibitor, trametinib. This drug targets the final steps of the gain-of-function activation of the RAS/MAPK pathway common to the causative NS genes. Mouse models of this drug to rescue mutant animals have led to its compassionate use in humans, although it is better known as a cancer therapy. In addition to the authors' detailed and successful use of trametinib (0.25mg/kg/d for 5 w) in their patient with a *PTPN11* class 5 variant, the paper's strength lies in its review of the 16 other cases given this drug since 2019. The findings reinforce the potential use of trametinib as a rescue therapy for critically ill patients with NS.

As found for the patient reported here (who had severe congenital pulmonary lymphangiectasia, chylothorax and hypoxia refractory to conventional management), in all 17 reported cases trametinib ameliorated the complications of lymphatic and/or cardiac disease. The case series includes patients with diverse genetic causes of NS. The majority were treated in the neonatal period or in early infancy (13/17), with differing exposure times to drug (5 w – 2 y) and differing periods of follow-up, off or on therapy (maximum 2 y). Of the series, 13/17 were noted to be stable and now at home. No universal efficacy criteria were defined, and 3 of 17 patients died– one who was withdrawn from therapy because of treatment failure, one because of a probable hypertrophic cardiomyopathic arrythmia following treatment with resolution of the congenital lymphangiectasia, and one with a non-NS related condition (pulmonary capillary hemangiomatosis), possibly related to the treatment. Long term outcome studies are lacking, and it will be important to build an international collaboration in order to pool clinical experience, define protocols and monitor safety.

Reference

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2.6. Mapping variants in thyroid hormone transporter MCT8 to disease severity by genomic, phenotypic, functional, structural and deep learning integration

Stefan Groeneweg, Ferdy S. van Geest, Mariano Martín, Mafalda Dias, Jonathan Frazer, Carolina Medina-Gomez, et al.
Nat Commun 2025 Mar 12;16:2479.
doi: 1038/s41467-025-56628-w

Brief Summary: This international consortium (53 sites, 23 countries) has been investigating the X-linked disease (1:70,000 males) caused by rare variants in the *MCT8* transmembrane transporter. The transport of

thyroid hormones depends on this molecule in many tissues, including the brain, and when it is defective, there are a wide range of clinical manifestations which include central hypothyroidism, developmental delay, and chronic peripheral thyrotoxicosis. Severe forms result in very compromised survival, with death before age 30.

This study assembled a comprehensive description of the genetics, neurodevelopment, and clinical/biochemical phenotype in 371 patients with *MCT8* defects. It describes genotype-phenotype associations which explain divergent presentations of the disease. They characterise both disease-causing variants and other non-synonymous common variants from population studies that maintained normal to only minimal decreases in transporter activity. A total of 8151 *MCT8* variants were classified according to severity, and their association to survival and to 24 of 32 disease features was examined. This deep phenotyping will permit more personalised anticipatory guidance.

The T3 analogue tri-iodothyroacetic acid (Triac) has been used, because smaller trials show that it ameliorates the peripheral hyperthyroidism and decreases TSH. This paper reports real world efficacy of Triac in 80 patients, showing that thyrotoxic symptoms are improved irrespective of the underlying phenotype. Structural modeling identified a 'linker' region in the protein containing mutation hotspots, and thus could be an important target for developing small molecules to correct aberrant transporter activity. But the most important aspect of this work is disease awareness: investigation of hypotonic newborns should always include TSH and thyroid hormones even if their interpretation may not always be clear, particularly if there is hypomyelination for age. This latter should prompt immediate genetic testing, including for *MCT8*.

Genomic Screening, New Gene Associations

2.7. Population-based, first-tier genomic newborn screening in the maternity ward

François Boemer, Kristine Hovhannesyan, Flavia Piazzon, Frédéric Minner, Myriam Mni, Valérie Jacquemin, Davood Mashhadizadeh, Noor Benmhammed, Vincent Bours, Adeline Jacquinet, Julie Harvengt, Saskia Bulk, Vinciane Dideberg, Laura Helou, Leonor Palmeira, Tamara Dangouloff, Baby Detect Expert Panel, Laurent Servais
Nat Med 2025 Apr 31(4):1339-1350.
doi: 10.1038/s41591-024-03465-x

Brief Summary: Newborn screening (NBS) is rapidly expanding in developed countries to include more rare diseases that can be treated successfully if identified early, as long as the criteria for adding them includes a reliable and cost-effective analytical method. This paper reports the first 18 months results in 3,847 screened babies (M=F) from the Belgian observational study, *BabyDetect* (ClinicalTrials.gov:NCT05687474), which uses a gene panel of ~400 genes (165 diseases) and an algorithm that discards those likely benign and variants of unknown significance. ~4,000-11,000 variants were inferred for each baby; only variants known to be associated with disease were reported. Direct cost was 365 Euros per baby, and turnaround time by the end of study period was 51 days. If a conventional NBS test was not available for comparison, reanalysis added an additional 3 weeks.

Main findings:A total of 71 cases were flagged for a pathogenic variant; only 41/71 were reported through conventional NBS. 44/71 had glucose-6-phosphate dehydrogenase deficiency. Only 1 false negative was recorded because the pathogenic variant did not appear in their curated list (it was added subsequently). Of the 30 cases not reported through NBS, they were all actionable but with varying degrees of intervention necessary since: 1) some caused milder disease phenotypes, 2) some were actionable through preventive measures or 3) some required surveillance. The challenges are multiple including complex analytic algorithms, enormous data storage capacity, the need to continually revise variant lists and the people power necessary to oversee result transmission and patient care, including counselling. But genomic newborn screening has undoubtedly begun, at least in countries that can afford it.

2.8. Rare variant associations with birth weight identify genes involved in adipose tissue regulation, placental function and insulin-like growth factor signalling

Katherine A. Kentistou, Brandon E. M. Lim, Lena R. Kaisinger, Valgerdur Steinthorsdottir, Luke N. Sharp, Kashyap A. Patel, Vinicius Tragante, Gareth Hawkes, Eugene J. Gardner, Thorhildur Olafsdottir, Andrew R. Wood, Yajie Zhao, Gudmar Thorleifsson, Felix R. Day, Susan E. Ozanne, Andrew T. Hattersley, Stephen O'Rahilly, Kari Stefansson, Ken K. Ong, Robin N. Beaumont, John R.B. Perry, Rachel M. Freathy

Nat Commun 2025 Jan 14;16(1):648.
doi: 10.1038/s41467-024-55761-2

Brief Summary: This study used whole exome sequencing of the UK Biobank cohort to identify maternal or fetal genes with rare variants impacting on birth weight. Fetal gene contributions were examined in up to 234,675 samples with a reported birth weight, and maternal gene contributions were studied in up to 181,883 females who had reported the birth weight of their first child. Independent confirmatory data was obtained from up to 45,622 Icelandic exomes, as well as GWAS common variant associations lying within 300 kb of their identified genes.

Eight genes with rare, deleterious loss of function mutations in the fetus (minor allele frequency $< 0.1\%$) were identified to impact on birth weight (*ACVR1C, IGF1R, INHBE, NOS3, NRK, NYNRIN, PAPPA2, PPARG*). For the maternal genes, 3 showed significance (*IGF1R, NOS3* - also in fetus and *ADAMTS8*). Teasing out whether maternal effects also correlated with their effects in the fetus sharing the same genotype, they noted *ACVR1C, INHBE, NRK, NYNRIN, PPARG* showed evidence of only fetal genotype effects, *IGF1R, PAPPA2, and NOS3* were classified as both fetal- and maternal-acting, and *ADAMTS8* the only maternal-acting gene. Sex-specificity was seen for stronger *PPARG* effects on female fetuses. Biologic plausibility is notable for all their genes. The most obvious are the known regulators of fetal-placental growth through IGF bioactivity; *IGF1R, PAPPA2* have been associated with several anthropometric measures and IGF-1 levels, with animal data and with human rare variants also strengthening the direct link. Their other key genes have been found associated with adult height, blood pressure, adipose tissue differentiation and regulation as well as likely involved in placental development/function.

This work gives insights that will no doubt be useful for better understanding fetal growth and long-term health.

2.9. Sex dimorphic associations of Prader–Willi imprinted gene expressions in umbilical cord with prenatal and postnatal growth in healthy infants

Berta Mas-Pares, Gemma Carreras-Badosa, Ariadna Gomez-Vilarrubl, Antonio De Arriba-Munoz, Olivia Lafalla-Bernard, Anna Prats-Puig, Francis De Zegher, Lourdes Ibañez, Andrea M. Haqq, Judit Bassols, Abel Lopez-Bermejo

World J Pediatr 2025 Jan;21(1):100-112.
doi: 10.1007/s12519-024-00865-4

Brief Summary: This study examined the association of multiple genes located in the Prader-Willi Syndrome locus on the growth of healthy children, using real-time PCR in umbilical cord tissue to look at relative gene expression. The genes tested included *MAGEL2*, *NDN*, and *SNURF-SNRPN*, and the small nucleolar RNAs *SNORD116* and *SNORD115;* all of these are exclusively transcribed from the paternal allele. It is already known that paternally expressed genes tend to favor prenatal growth and that several of the genes in the PWS locus are expressed in the hypothalamus and regulate appetite, GH secretion, and puberty.

122 healthy newborns (59F, 63M) were recruited from Northern Spain following a normal conception, pregnancy and delivery. Anthropometric assessments were performed at birth and in follow-up at several time points (9) up to age 6 years. *MAGEL2*, *NDN*, *SNORD116*, and *SNORD115* expression in umbilical cord tissue was negatively associated with birthweight, length, and placental weight; these associations were stronger in girls. After birth, these genes were positively associated with growth, with a stronger association in boys. *MAGEL2*, *SNORD116*, and *SNORD115* expression predicted early postnatal growth, explaining the higher growth rate in boys compared to girls and accounting for sex differences of up to 1.5 kg in weight and 3 cm in height during infancy. Key insights from this paper suggest that the Prader-Willi Syndrome locus may be important for post-natal growth and sexual dimorphism in growth.

2.10. Successful transition to sulfonylurea for relapsed monogenic diabetes due to rare 6q23.3 duplication

Hassan D., Allen DB., Chen M.
JCEM Case Rep 2024 Oct 16;2(10):luae180.
doi: 10.1210/jcemcr/luae180

Brief Summary: This paper describes a female born SGA with transient neonatal diabetes (TNDM)[1] due to a 6q23.3 duplication. It is one of only a few published cases, and the first case who transitioned to sulfonylurea when diabetes relapsed. She was treated with insulin until age 4 months and then again after relapse as an adolescent. At age 15y 3m, she developed diabetic ketoacidosis and was negative for antibodies to GAD-65, IA2 and ZN transporter 8. After a 3-month period on insulin, she was successfully transitioned to glyburide and has maintained a normal HbA1c (5.5-5.7) on this medication during the 17 months of follow-up to date. She had global developmental delay and was delayed scholastically by 8 years. She had several facial dysmorphisms, but no macroglossia or umbilical hernia. Whole exome sequencing or a targeted monogenic diabetes gene panel was not performed. Interestingly, when her 6q23.3 duplication was diagnosed in infancy (in 2007), it was noted as a variant of unknown significance.

The most frequent cause (60-70%) of TNDM is over expression of normally imprinted genes within a critical region on 6q. The most common mechanism is paternal UPD of chromosome 6 followed by a 6q24 duplication and rare hypomethylation of the maternal genes in the TNDM locus.

The critical 6q region for TNDM is 6q23-24 and implicates the paternally expressed *PLAGL1* (pleiomorphic adenoma gene-like 1), and *HYMAI* (hydatidiform mole associated imprinted,within the same domain). Animal data and patient reports suggest that with these duplications, beta cells retain insulin reserves but have decreased sensitivity to glucose.

Main points from this case are that sulfonylureas may be useful for treating both TNDM *and* relapsing diabetes in cases of 6q23-24 duplications, although the duplication subtypes, additional genetic loci and epigenetic factors may modify the response.

Reference

1. Greeley SAW et al. ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes*. 2022 Dec;23(8):1188-1211. doi: 10.1111/pedi.13426.

2.11. Transient diabetes mellitus with *ABCC8* variant successfully treated with sulfonylurea: two case reports and review of literature

Ling-Hua Shen, Yan Cui, Dong-Xia Fu, Wei Yang, Sheng-Nan Wu, Hui-Zhen Wang, Hai-Hua Yang, Yong-XingChen, Hai-Yan Wei
World J Diabetes 2024 August 15;15(8): 1811-1819.
doi: 10.4239/wjd.v15.i8.1811

Brief Summary: This paper presents 2 cases of transient neonatal diabetes mellitus (TNDM)[1] due to a novel gain-of-function heterozygous missense variant in *ABCC8* (c.3880C > T); these are added to the 10 previously described cases where sulfonylurea therapy has been used, also summarised here. This defect, along with other rare variants in *KCNJ11*, are the second most common cause of TNDM.

Their patients, born AGA with no dysmorphisms, presented at ages 2m and 7m with post-infectious DKA and were negative for multiple diabetes-specific antibodies. Both infants were successfully treated with oral glyburide, following a short course of insulin. No major side effects were noted, and they were able to stop after 1 month in the first case, and after 1 year in the second case.

There are > 700 pathogenic or likely pathogenic variants in *ABCC8,* which encodes the sulfonylurea receptor 1 of the ATP-sensitive potassium channel in pancreatic beta cells. Previous series have shown that most cases present by age 6 m, although 5-8% can occur after age 1y. These authors conclude from their cases, and the others with *ABCC8* gain-of-function variants who were transitioned to oral sulfonylureas, that we are far from

being able to predict responses to this therapy. The rationale for its use is clear: the mutated multimeric K-ATP channel is unable to release insulin, but sulfonylureas act by targeting the SUR1 subunits, promoting channel closure and thus insulin release. Our ability to predict not only response to sulfonylurea therapy but also whether diabetes will be transient, relapse if initially transient, or be permanent will await additional strides in personalised medicine, when genotype-phenotype associations and the contribution of other loci beyond the NDM loci identified to date become clearer.

Reference

1. Greeley SAW et al, *Pediatr Diabetes*. 2022 Dec;23(8):1188-1211. doi: 10.1111/pedi.13426. ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and management of monogenic diabetes in children and adolescents

2.12. Non-coding *CIS*-regulatory variants in *HK1* cause congenital hyperinsulinism with variable disease severity

Jasmin J. Bennett, Cecile Saint-Martin, Bianca Neumann, Jonna M. E. Mannisto, Jayne A. L. Houghton, Susann Empting, Matthew B. Johnson, Thomas W. Laver, Jonathan M. Locke, Benjamin Spurrier, Matthew N. Wakeling, Indraneel Banerjee, Antonia Dastamani, Huseyin Demirbilek, John Mitchell, Markus Stange, International Congenital Hyperinsulinism Consortium, Klaus Mohnike, Jean-Baptiste Arnoux, Nick D. L. Owens, Martin Zenker, Christine Bellanne-Chantelot, Sarah E. Flanagan

Genome Med 2025 Mar 3;17(1):17.

doi: 10.1186/s13073-025-01440-w

Brief Summary: These investigators from genome centers in Exeter, UK, Paris, France and Magdeburg, Germany screened a cis-regulatory region of *HK1*(hexokinase 1) in 1761 probands with hyperinsulinism of unknown aetiology, to determine the frequency of this recently described genetic cause of congenital hyperinsulinism. *HK1* is normally not expressed in pancreas or liver but is active in all other human tissues. Its aberrant reactivation in pancreatic tissue leads to abnormal glucose sensing and insulin secretion in the face of low plasma glucose. Large deletions, smaller insertions or deletions and single nucleotide variants in a 46 bp intronic region of *HK1* can lead to *HK1* transcription and thus cause autosomal dominant hyperinsulinism. An *HK1* variant was found in 89/1761 (5%) probands and in 63 family members. This compares to a frequency of 3% in a Norwegian cohort[1] and 9% in a previous UK series[2] (162 probands also included in this paper).

Hyperinsulinism had a variable onset, between birth and 26 y (median 7 days, 16% childhood, 4% adult onset). Median birth weight Z-score and IQR was 0.48 [-0.12-1.97] . Treatment was variable: 77% received diazoxide, 8% somatostatin receptor analogue, 15% both drugs and 20% required pancreatic surgery. Evolution varied from spontaneous remission to hypoglycemia persisting into adulthood. They describe variable penetrance in 8 probands, whose transmitting parent was asymptomatic, and phenotypic variability between and within families for the same variants.

These results place *HK1*among the major causes of hyperinsulinemic hypoglycemia. Non-coding regions in at least 3 other genes have been found to cause hyperinsulinism, reinforcing the importance of the non-coding genome to disease.

References

1. Velde CD et al, Clinical and Genetic Characteristics of Congenital Hyperinsulinism in Norway: A Nationwide Cohort Study. *J Clin Endocrinol Metab* 2025 Jan 21;110(2):554-563. doi: 10.1210/clinem/dgae459.
2. Wakeling MN et al, Non-coding variants disrupting a tissue-specific regulatory element in HK1 cause congenital hyperinsulinism. *Nat Genet*. 2022;54(11):1615-1620. doi: 10.1038/s41588-022-01204-x.

2.13. Neonatal hyperinsulinism: a retrospective study of presentation and management in a tertiary neonatal intensive care unit in the UK

Kalogeropoulou M.S., Couch H., Thankamony A., Beardsall K.

Arch Dis Child Fetal Neonatal Ed. 2025 Apr 17;110(3):261-268.

doi: 10.1136/archdischild-2024-3273221

Brief Summary:This retrospective study evaluated the clinical presentation and management diversity of 99 neonates diagnosed with hyperinsulinism in a UK tertiary neonatal unit from 2015–2021. The cohort was categorized into three severity groups: severe (20%), moderate (30%), and mild (50%). Diagnosis was based on blood glucose <2.8 mmol/L and insulin >6 pmol/L. Although hyperinsulinism is typically linked with large for gestational age (LGA) infants, 35% were small for gestational age (SGA) and 42% were preterm, showing a broader clinical spectrum. Notably, glucose requirements and severity did not consistently correlate with gestational age or birth weight. Diazoxide treatment was initiated in 20 infants, with term infants receiving it earlier than preterms (9.9 vs. 37 days). Severe cases received higher concentrations of dextrose and had longer hospital stays. Genetic testing was more frequent in severe cases (90%), yielding a diagnosis in 35%. Only 23% were referred to national specialists, and 3% transferred. Despite high early glucose needs, only a minority showed persistent hyperinsulinism requiring diazoxide.

The study underscores the need for early clinical consideration of hyperinsulinism across all birth weights and gestational ages and calls for prospective studies to guide standardized care and evaluate long-term outcomes.

Fetal Exposure to GLP-1 Agonists and Oral Hypoglycemic Agents

2.14. Maternal GLP-1 receptor activation inhibits fetal growth

Liping Qiao, Cindy Lu, Tianyi Zang, Brianna Dzyuba, Jianhua Shao

Am J Physiol Endocrinol Metab 2024 Mar 1;326(3):E268-E276.
doi: 10.1152/ajpendo.00361.2023

Brief Summary: C57BL/6 mice were used to study the effects of maternal GLP-1 on dams and their fetuses. Circulating levels of GLP-1 (produced by intestinal L-cells) were seen to decline over gestation despite maintenance of L-cell population. Administration of semaglutide (GLP-1RA) in late pregnancy (E13.5 to E17.5) led to a decrease in appetite, insulin levels and glucose but weight of dams was increased normally. Significant and progressive decreases were noted in fetal weights by E18.5 even when maternal blood glucose was restored, and if anything, circulating fetal IGF-1 levels were increased, perhaps as a compensatory mechanism. Placental weight was unchanged but placental histology and vascularisation was altered as was placental expression of important nutrient transporters including glucose transporter 1 and sodium-neutral amino acid transporter 1; these findings may be responsible for the effect on fetal weight. They conclude that modulation of circulating GLP-1 is very important during pregnancy, and that GLP-1RA has inhibitory effects on placental development and growth and thus on fetal weight, perhaps through placental GLP-1 receptors noted by others to be on mouse endothelial cells and human trophoblast cells. Of note, they previously showed the importance of mouse pancreatic α-cells in controlling maternal metabolic adaptation to pregnancy through enhanced insulin secretion using an inducible Cre/loxp ablation to create an α -null mouse before and during pregnancy. Enteroendocrine L-cells and circulating GLP-1 were maintained in the normal range[1], so clearly intra-pancreatic and circulating GLP-1 must be considered separately when teasing out the role of GLP-1 during pregnancy, and ultimately, the impact of GLP-1RA therapy.

As recently stated in an opinion paper[2], evidence is lacking to support use of GLP-1RA during pregnancy or even to counsel patients about peri-conceptional exposure. It is wise to counsel use of contraception during GLP-1RA therapy. The mouse data in this paper would certainly support this approach.

References

1. Qiao L et al, The Essential Role of Pancreatic a-Cells in Maternal Metabolic Adaptation to Pregnancy *Diabetes* 2022;71(5):978-988. doi: 10.2337/db21-0923.
2. Varughese SM et al, GLP-1 receptor agonist therapy and pregnancy: Evolving and emerging evidence *Clinical Medicine* 2025;25(2):100298. doi: 10.1016/j.clinme.2025.100298.

2.15. Oral glucose-lowering agents vs insulin for gestational diabetes: a randomized clinical trial

Doortje Rademaker, Leon de Wit, Ruben G. Duijnhoven, Daphne N. Voormolen, Ben Willem Mol, Arie Franx, et al.
JAMA. 2025;333(6):470–478.
doi: 10.1001/jama.2024.23410

Brief Summary: This randomized noninferiority trial evaluated whether a sequential oral glucose-lowering strategy (metformin, followed by glyburide if needed) is noninferior to insulin in preventing large-for-gestational-age (LGA) infants in gestational diabetes.

Conducted at 25 Dutch centers with 820 participants between 16–34 weeks of gestation, all had inadequate glycemic control on dietary management. Participants were randomized to oral agents (n = 409) or insulin (n = 411). Metformin was initiated and up-titrated, with glyburide added if targets were not met. Primary outcome was infants born LGA (>90th percentile). LGA occurred in 23.9% of infants in the oral agent group vs 19.9% in the insulin group (absolute risk difference, 4.0%; 95% CI: −1.7% to 9.8%); the upper confidence interval exceeds the predefined noninferiority margin, 8%. Notably, 79% of women in the oral agents arm maintained glycemic control without requiring insulin. However, maternal hypoglycemia occurred more often with oral agents (20.9% vs 10.9%). No significant differences were found for other secondary outcomes, including caesarean delivery, preterm birth, or neonatal complications.

This study suggests that while most women managed gestational diabetes successfully with oral agents, the strategy did not meet statistical criteria for noninferiority to insulin in preventing LGA births. Findings support continued prioritization of insulin therapy for optimal perinatal outcomes.

2.16. Metformin and risk of adverse pregnancy outcomes among pregnant women with gestational diabetes in the United Kingdom: a population-based cohort study

Yu YH., Platt RW., Reynier P., Yu OHY, Filion KB.
Diabetes Obes Metab. 2025;27(2):976–986.
doi: 10.1111/dom.16115

Brief Summary: This population-based retrospective cohort study investigated whether initiating metformin instead of insulin after 20 weeks of gestation affects adverse pregnancy outcomes among women with gestational diabetes mellitus (GDM). The study used data from the UK Clinical Practice Research Datalink and Hospital Episode Statistics from 1998 to 2018, including 2,192 singleton pregnancies (1,297 on metformin; 895 on insulin).The primary outcome was a composite of large for gestational age (LGA) and macrosomia.

Key Findings include: 1) Compared to insulin initiation, metformin was associated with a lower risk of LGA infants and macrosomia (HR 0.64; 95% CI 0.49–0.78). 2) Metformin was also linked to reduced risk of caesarean delivery (HR 0.83; 95% CI 0.69–0.98) and a trend to lower risk of preterm birth (HR 0.83; 95% CI 0.58–1.08). 3) No difference was found in hypertensive disorders of pregnancy (HR 0.92; 95% CI 0.57–1.27). 4) Risk of SGA infants appeared higher with metformin, although not statistically robust (HR 1.33; 95% CI 0.67–2.00). 5) Sensitivity analyses, including per-protocol, high-dimensional propensity score adjustment, and bias models, confirmed the robustness of primary findings.

The study provides real-world evidence supporting metformin as a potentially safer, effective alternative to insulin in the treatment of GDM, especially in cases where insulin adherence is poor. However, the possible increased risk of SGA births as well as the previously summarised study suggesting that oral hypoglycemic agents do not significantly reduce the risk of LGA birthcalls for further investigation. Individualized risk benefit assessment remains essential when considering metformin in pregnancy.

PCOS and Birth Outcome

2.17. Systematic review and meta-analysis of birth outcomes in women with polycystic ovary syndrome

Mahnaz Bahri Khomami, Somayeh Hashemi, Soulmaz Shorakae, Cheryce L. Harrison, Terhi T. Piltonen, Daniela Romualdi, Chau Thien Tay, AyaMousa, Eszter Vanky, Helena J. Teede
Nature Communications. July 2024; 15:5592.
doi: 10.1038/s41467-024-49752-6

Brief Summary: Given the increasingly frequent use of metformin during pregnancies characterised by PCOS as well as other confounders affecting birth outcomes, these investigators sought to determine whether PCOS is an independent risk factor. They also investigated to what extent other maternal characteristics such as BMI and assisted reproductive technology (ART) influence these associations. This systematic review and meta-analysis of 73 studies included 92,881 offspring of women with and without PCOS.

Key findings from this comprehensive study are: 1) Women with PCOS were on average younger but had higher BMI and gestational weight gain. 2) The odds of preterm birth were higher in PCOS (OR: 1.53), consistent across ART and high-quality prospective studies, but attenuated when matched for age and BMI. 3) Mean birthweight was lower in PCOS offspring (MD: −57.87g), and the odds of low birth weight were increased (OR: 1.28). 4) PCOS was associated with higher odds of fetal growth restriction (OR: 1.84), but not small for gestational age (SGA) except in age/BMI-matched subsets, where SGA odds increased (OR: 2.91). 5) The odds of macrosomia and large for gestational age were no different, suggesting a complex interplay between factors promoting both restricted and excessive fetal growth.

This study emphasizes the need for PCOS recognition in pregnancy care due to increased risks in offspring, particularly related to prematurity and impaired fetal growth independent of treatment modalities. Strengths are its comprehensive design and subgroup analyses. These findings informed the 2023 International PCOS Guidelines, emphasizing the importance of considering PCOS as a relevant factor in perinatal risk assessment.

Ambiguous Genitalia

2.18. Ambiguous genitalia due to 3β-Hydroxysteroid dehydrogenase type 2 deficiency: clinical, genetic, and functional characterization of two novel *HSD3B2* variants

Jani Liimatta, Kay Sauter, Therina du Toit, André Schaller, Dagmar l'Allemand, Christa E. Flück
JCEM Case Rep. 2025 Jan 20;3(2):luae245.
doi: 10.1210/jcemcr/luae245

Brief Summary: This case report describes a 46,XY neonate born with ambiguous genitalia in whom 2 novel heterozygous variants in the HSD3β2 gene were found (c.779C > T/p.Pro260Leu and c.307 + 1G > A/p.Gly103Asp,fs29X), but only after age 5 y when she presented with premature pubarche and adrenarche, relative tall stature and +1.8 y advanced bone age. These novel variants were validated *in vitro* in transfected cells.

The midwife and pediatrician attending this infant after birth had noted increased 17-hydroxyprogesterone on neonatal screening, an External Genital Score of 6.5/12 with a 2.2 cm genital tubercle, scrotal hypospadias and echographically normal labioscrotal gonads with no uterus. Female sex of rearing was recommended. There was no evidence of adrenal failure and steroid studies in infancy, including mass spectroscopy (LC/GC MS), did not confirm a specific diagnosis.

At age 5 y, electrolytes, ACTH, testosterone and DHT remained normal, serum aldosterone was very low, and DHEA and DHEAS were elevated. A 0.25 mg Synacthen test showed an increased DHEA/androstenedione ratio– the clue to the enzymatic block - along with suggestive LC/GC-MS steroid features. Hydrocortisone (10 mg/m^2/d) and fludrocortisone (0.05 mg/d) treatment was initiated. At age 7 y, the DSD team noted midpubertal

status (P3, G3), stretched phallus length 6 cm, no gynecomastia, continued BA advancement but a predicted height within genetic target. There was no gender dysphoria although it was noted that the counselling was particularly sensitive given the extent of virilisation and context of autism and cognitive and language delay; options for management will continue to be discussed.

The most important contribution of this case report, besides adding novel, rigorously tested disease-causing variants in HSD3β2, is the excellent differential diagnostic table, and the discussion of the pitfalls involved in steroid measurements, particularly when there is some retention of enzyme activity as in this patient.

3. Thyroid

Paul van Trotsenburg[1], Dilek Bingöl Aydin[2]
[1]Amsterdam, The Netherlands; [2]Istanbul, Turkey (YES member)

Introduction

In the past year, many publications have appeared on disorders of the thyroid gland or the hypothalamus-pituitary-thyroid (HPT) axis in children and adults. Here, you will find a selection of publications in this field of importance to the discipline of pediatric endocrinology, published in the period June 2025 to July 2025, Here are a few quotes to pique your interest:

"Cryogenic-sample electron microscopy unravels the structure of monocarboxylate transporter 8", "Identification and characterization of highly potent and isoenzyme-selective inhibitors of deiodinase type I via a nonradioactive high-throughput screening method: lead compounds in developing strategies to combat hyperthyroidism", "Unraveling the molecular architecture of autoimmune thyroid diseases at spatial resolution", "Population-based sibling control study Swedish adolescents with congenital hypothyroidism highlights the importance of early detection and treatment of mild cases of CH to support cognitive and academic development", "Clinical study describes 8 female patients with heterozygous pathogenic variants in *SLC16A2*, the gene causing MCT8 deficiency (Allan-Herndon-Dudley syndrome), previously thought to affect only males", "New reference values for thyroid volume by ultrasound in German children and adolescents from a population-based study".

Mechanism of the Year

3.1. Molecular mechanism of thyroxine transport by monocarboxylate transporters

Tassinari M, Tanzi G, Maggiore F, Groeneweg S, van Geest FS, Freund MET, Stavast CJ, Boniardi I, Pasqualato S, Visser WE, Coscia F

Nat Commun. 2025 May 14;16(1):4493.
doi: 10.1038/s41467-025-59751-w. PMID: 40368961

Brief Summary: Using cryo-electron microscopy, this basic/translational experimental study determined structures of monocarboxylate transporter 8 (MCT8) and MCT10 in multiple transport states: ligand-free MCT8, T4-bound MCT8, silychristin-bound MCT8, a pathogenic MCT8-D424N mutant, and T4-bound MCT10. The study identified critical (single amino acid) residues: R371 (electrostatic coordination), N119 and D424 (gate closure and conformational coupling), that are essential for thyroxine binding and translocation. Silychristin inhibits MCT8 by locking it in an outward-facing state. These findings clarify the molecular mechanism of thyroid hormone transport and explain transport failure in MCT8 deficiency despite preserved T4 binding.

This study provides the first high-resolution structural insight into how thyroid hormones are transported by MCT8 and MCT10, which is critical for understanding intracellular thyroid hormone availability. By identifying specific residues essential for transport—and showing how a pathogenic, disease-causing MCT8 variant disrupts this process, the study elucidates the molecular basis of MCT8 deficiency. Furthermore, it reveals how the flavonolignan silychristin inhibits MCT8, offering a structural framework for future drug design targeting thyroid hormone transporter disorders.

Basic Science

3.2. Identification and characterization of highly potent and isoenzyme-selective inhibitors of Deiodinase type I via a nonradioactive high-throughput screening method

Sane R, Seyffarth C, Kleissle S, Neuenschwander M, von Kries JP, Frädrich C, Renko K, Wirth EK, Köhrle J
Thyroid. 2025 May;35(5):576-589.
doi: 10.1089/thy.2025.0036. PMID: 40170637

Brief Summary: This experimental study developed a nonradioactive high-throughput assay to identify type 1 deiodinase (DIO1) inhibitors, addressing the lack of selective tools to study or target DIO1 clinically. Given DIO1's role in T3 production, selective inhibition may benefit patients with severe hyperthyroidism. Of 69,344 low-molecular-weight compounds screened, 15 were identified as novel, highly potent, and selective DIO1 inhibitors with nanomolar IC_{50} values. Eight of these 15 also inhibited DIO1 in intact cells. This platform enables discovery of thyroid hormone metabolism modulators for research and therapy.

This study addresses a critical gap in thyroid hormone research by enabling the discovery of potent and selective inhibitors of DIO1, a key enzyme in T3 production. Until now, tools to selectively target DIO1 have been lacking, limiting the ability to study its physiological and pathological roles. By developing a scalable nonradioactive assay and identifying cell-active inhibitors, this study opens the door to targeted modulation of thyroid hormone metabolism in conditions like severe hyperthyroidism.

3.3. Unraveling the molecular architecture of autoimmune thyroid diseases at spatial resolution

Martínez-Hernández R, Sánchez de la Blanca N, Sacristán-Gómez P, Serrano-Somavilla A, Muñoz De Nova JL, Sánchez Cabo F, Heyn H, Sampedro-Núñez M, Marazuela M
Nat Commun. 2024 Jul 13;15(1):5895.
doi: 10.1038/s41467-024-50192-5. PMID: 39003267

Brief Summary: This translational studyapplied spatial transcriptomics and single-cell RNA sequencing to thyroid tissue from 3 Hashimoto's thyroiditis (HT) patients, 3 Graves' disease (GD) patients, and 2 controls. They identified shared features, including antigen-presenting thyrocytes with upregulated CD74 and MIF, as well as disease-specific stromal signatures: $ADIRF^+$ myofibroblasts and $PLVAP^+$ endothelial cells in GD, and inflammatory fibroblasts in HT. These epithelial and stromal subtypes may contribute to the pathogenesis and heterogeneity of autoimmune thyroid diseases.

This study provides spatial and cellular analyses of thyroid tissue architecture in autoimmune thyroid disease (AITD), showing how thyrocytes, immune cells, fibroblasts, and endothelial cells interact in situ. By distinguishing disease-specific stromal and epithelial signatures in Hashimoto's thyroiditis (HT) and Graves' disease (GD), it advances our understanding of AITD heterogeneity and pathogenesis. These novel insights may support the development of targeted diagnostics and therapies, particularly relevant to individualized approaches in pediatric and early-onset autoimmune thyroid conditions.

Congenital Hypothyroidism

3.4. Congenital hypothyroidism and school achievement in adolescence: a population-based sibling control study

Gunnerbeck A, Lundholm C, von Döbeln U, Zetterström RH, Almqvist C, Nordenström A
J Pediatr. 2024 Dec:275:114240.
doi: 10.1016/j.jpeds.2024.114240. PMID: 39151600

Brief Summary: This population-based sibling control study assessed school performance in Swedish adolescents with congenital hypothyroidism (CH) born between 1982 and 1997; in this period, the threshold for an abnormal newborn screening for CH test was lowered from 25 mU/L blood to 20 mU/L blood. Among 923 CH patients, 448 were identified via newborn screening (DBS) and treated with levothyroxine (LT4) subsequently ($DBS^+/LT4^+$), and 475 were treated for CH (ICD) but were not detected by screening ($DBS^-/ICD^+/LT4^+$). Compared with the general population and siblings, adolescents in the $DBS^+/LT4^+$ group had similar academic outcomes, while those in the $DBS^-/ICD^+/LT4^+$ group showed lower grades in core subjects and reduced eligibility for upper secondary education.

In essence, Gunnerbeck et al replicated the findings of Lain et al who found that Australian infants with neonatal TSH levels just below the then applied newborn screening thresholds, who were typically not diagnosed or treated, had an increased risk of poor educational and developmental outcomes [1].Both studies highlight the importance of early detection and treatment of mild cases of CH to support cognitive and academic development.

Reference

1. Lain SJ, Bentley JP, Wiley V, Roberts CL, Jack M, Wilcken B, Nassar N. Association between borderline neonatal thyroid-stimulating hormone concentrations and educational and developmental outcomes: a population-based record-linkage study. Lancet Diabetes Endocrinol. 2016 Sep;4(9):756-765. doi: 10.1016/S2213-8587(16)30122-X. PMID: 27453174.

3.5. Identification of eukaryotic translation initiation factor 4B as a novel candidate gene for congenital hypothyroidism

Sun F, Zhang RJ, Fang Y, Yan CY, Zhang CR, Wu FY, Yang RM, Han B, Song HD, Zhao SX
J Clin Endocrinol Metab. 2024 Nov 18;109(12):3282-3292.
doi: 10.1210/clinem/dgae270. PMID: 38654471

Brief Summary: This study identifies the eukaryotic translation initiation factor *EIF4B* as a novel candidate gene for congenital hypothyroidism (CH). A de novo *EIF4B* variant (P328L) was discovered through whole-exome sequencing in 192 CH patients. The authors used patient-derived data, in vitro translation assays, and in vivo zebrafish and mouse models to assess its functional role.

In zebrafish, *EIF4B* knockdown produced two phenotypic classes. Severely affected embryos exhibited short body length, notochord and tail defects, bradycardia, and reduced eye and ear size, features consistent with hypothyroidism and developmental delay. These embryos showed low thyroid hormone levels, abnormal thyroid morphology, and elevated expression of the thyroid-stimulating hormone subunit βa (TSHBA). T4 supplementation partially rescued heart rate, body length, and TSHBA levels, implicating a thyroid-specific mechanism. However, persistent eye and ear abnormalities suggested additional non-thyroidal effects.

In mice, complete loss of *Eif4b* caused perinatal lethality, while heterozygous animals appeared phenotypically normal, indicating a dosage-sensitive requirement for *EIF4B*. Histology confirmed structural thyroid abnormalities in homozygous mutants.

Mechanistically, *EIF4B* was shown to regulate translation of key thyroid developmental genes. The P328L variant reduced translation efficiency of *NKX2-1* and *TPO*, with a trend toward reduced TG translation, suggesting *EIF4B* facilitates mRNA translation of essential thyroid genes.

Transcriptomic analysis revealed impaired thyroid cell migration and increased cell adhesion complex formation in the absence of EIF4B, proposing a novel mechanism for thyroid dysgenesis beyond traditional defects in hormone synthesis or migration genes.

In conclusion, this study links translational control and cellular dynamics to thyroid development, expands the genetic landscape of CH, and highlights *EIF4B* as a diagnostic candidate. It underscores the value of integrating patient genomics with functional modeling to uncover new disease mechanisms in congenital thyroid disease.

3.6. MCT8 deficiency in females

Groeneweg S, van Geest FS, van der Most F, Abela L, Alfieri P, Bauer AJ, Bertini E, Cappa M, Çelik N, de Coo IFM, Dolcetta-Capuzzo A, Dubinski I, Granadillo JL, Hoefsloot LH, Kalscheuer VM, van der Knoop MM, Krude H, McNerney KP, Paone L, Peeters RP, Peters C, Schuelke M, Schweizer U, Sprague JE, van Trotsenburg ASP, Wilpert NM, Zanni G, van Zutven LJCM, Visser WE

J Clin Endocrinol Metab. 2025 May 27:dgaf311. Online ahead of print.
doi: 10.1210/clinem/dgaf311. PMID: 40420837

Brief Summary: This clinical study describes8 female patients with heterozygous pathogenic variants in *SLC16A2*, the gene causing MCT8 deficiency (Allan-Herndon-Dudley syndrome), previously thought to affect only males. All patients had variable neurocognitive impairment, behavioral problems and abnormal thyroid function abnormalities but, in contrast to male patients, only 2 had dystonia or spasticity, and hypotonia. 7 of the 8 studied women showed skewed X-chromosome inactivation, and in 5 of these 7 women functional studies showed impaired thyroid hormone transport in patient-derived fibroblasts. Compared to asymptomatic carriers, patients had higher (total) T3/rT3 and (total) T3/FT4 ratios.

This study highlights that MCT8 deficiency should be considered in females presenting with mild to moderate neurocognitive impairment, whether or not accompanied by psychiatric symptoms, and abnormal thyroid function tests, specifically low FT4 or T4 and elevated FT3 or T3.

3.7. Normal values for the fT3/fT4 ratio: centile charts (0-29 years) and their application for the differential diagnosis of children with developmental delay

Wilpert NM, Thamm R, Thamm M, Kratzsch J, Seelow D, Vogel M, Krude H, Schuelke M

Int J Mol Sci. 2024 Aug 6;25(16):8585.
doi: 10.3390/ijms25168585. PMID: 39201272

Brief Summary: This cross-sectional study establishes age- and sex-specific reference values for the serum fT3/fT4 ratio in individuals aged 0–29 years to aid in the diagnosis of 3 rare genetic disorders that affect thyroid hormone transport, metabolism, and action: MCT8 deficiency (SLC16A2), resistance to thyroid hormone α (THRA), and selenoprotein deficiency (SECISBP2). Using 23,522 fT3 and fT4 data points from 2 large healthy cohorts, percentile charts were generated and applied to 4 patient groups. The fT3/fT4 ratio was elevated in MCT8 and THRA patients, decreased in SECISBP2 deficiency, and normal in cerebral palsy.

The study highlights that the fT3/fT4 ratio may be more sensitive than fT3 or fT4 alone for detecting patients with THRA, SLC16A2, or SECISBP2 defects, as these individuals often have hormone levels within the normal range. It also emphasizes that children with unexplained developmental delay should not only be screened for primary and central hypothyroidism (via TSH and fT4), but also for rare thyroid hormone action defects by measuring fT3 and calculating the fT3/fT4 ratio.

3.8. 2024 European thyroid association guidelines on diagnosis and management of genetic disorders of thyroid hormone transport, metabolism and action

Persani L, Rodien P, Moran C, Visser WE, Groeneweg S, Peeters R, Refetoff S, Gurnell M, Beck-Peccoz P, Chatterjee K

Eur Thyroid J. 2024 Aug 3;13(4):e240125.
doi: 10.1530/ETJ-24-0125. PMID: 38963712

Brief Summary: This guideline from the European Thyroid Association (ETA) provides comprehensive, evidence-based recommendations for the diagnosis and management of genetic defects in thyroid hormone transport, metabolism, and action. Developed through systematic literature review and expert consensus, it covers

the differential diagnosis of elevated thyroid hormone levels with non-suppressed TSH, resistance to thyroid hormone β and α (RTHβ, RTHα), MCT8 deficiency, and SECISBP2-related thyroid hormone metabolism disorders. Key updates include diagnostic flowcharts, genotype–phenotype correlations, and treatment strategies, notably the use of TRIAC in MCT8 deficiency. The guideline aims to standardize care and improve outcomes in these rare conditions.

This guideline is an essential resource for pediatric endocrinologists managing children with unexplained thyroid hormone abnormalities.

Auto-Immune Thyroid Disease

3.9. The relationship between the gut microbiota and thyroid disorders

Ludgate ME, Masetti G, Soares P
Nat Rev Endocrinol. 2024 Sep;20(9):511-525.
doi: 10.1038/s41574-024-01003-w. PMID: 38906998

Brief Summary: This narrative review summarises emerging evidence linking gut microbiota composition to thyroid disorders, including autoimmune thyroid disease (AITD) and thyroid cancer. Drawing on both animal models and human studies, the authors explore how microbial metabolites, particularly short-chain fatty acids, affect immune regulation, thyroid hormone metabolism, and the formation or degradation of carcinogens. Although the number of human studies on AITD, including Graves' disease (with or without orbitopathy) and Hashimoto's thyroiditis, remains limited (N = 16), all report found significant alterations in gut microbial profiles. Identifying microbial species that promote or protect against disease pathogenesis, treatment response, and relapse could enable the development of personalized, microbiome-directed therapies.

This review provides an excellent overview of what is currently known about the role of the gut microbiota in AITD.

3.10. Early appearance of thyroid autoimmunity in children followed from birth for type 1 diabetes risk

Jonsdottir B, Clasen JL, Vehik K, Lernmark Å, Lundgren M, Bonifacio E, Schatz D, Ziegler AG, Hagopian W, Rewers M, McIndoe R, Toppari J, Krischer J, Akolkar B, Steck A, Veijola R, Haller MJ, Elding Larsson H; TEDDY Study Group
J Clin Endocrinol Metab. 2025 Jan 21;110(2):498-510.
doi: 10.1210/clinem/dgae478. PMID: 38996042

Brief Summary: This prospective cohort study from the TEDDY project followed 5,066 children with increased genetic risk for type 1 diabetes from birth through adolescence. It found that thyroid autoantibodies (TPOAb and/or TgAb) emerge as early as 10–15 months of age, with simultaneous seroconversion significantly increasing the risk of clinical thyroid disease.

The findings challenge the conventional view that autoimmune thyroid disease (AITD) is a later-onset condition by demonstrating that thyroid autoimmunity may begin well before school age in genetically at-risk children. A notable observation was the strong sex difference: girls had more than double the risk of developing thyroid autoimmunity compared to boys, even in early childhood, contrasting with previous reports suggesting minimal sex differences before puberty. A family history of AITD, particularly paternal, further increased risk, underscoring the roles of both sex and heritability.

Children who developed both TPOAb and TgAb simultaneously had a markedly higher risk of clinical thyroid disease (hazard ratio = 6.34) than those with single antibody positivity. Notably, the timing of simultaneous seroconversion was a stronger predictor of disease progression than the order in which antibodies appeared.

In the context of increasing autoimmune comorbidities among children, especially those at risk for type 1 diabetes, these findings support earlier and broader thyroid screening strategies in genetically susceptible populations. Early detection of thyroid autoimmunity could enable closer monitoring and timely intervention, potentially preventing complications such as growth retardation or cognitive deficits.

This study significantly advances our understanding of the early natural history and risk factors for AITD and highlights the importance of sex-specific and family history–guided surveillance in pediatric endocrinology.

3.11. Data-driven strategies for carbimazole titration: exploring machine learning solutions in hyperthyroidism control

Reich T, Bakirov R, Budka D, Kelly D, Smith J, Richardson T, Budka M

J Clin Endocrinol Metab. 2025 Mar 17;110(4):1105-1114.
doi: 10.1210/clinem/dgae642. PMID: 39271154

Brief Summary: This retrospective cohort study used machine learning (ML) approaches to improve carbimazole dose titration in patients with autoimmune hyperthyroidism. Using treatment data (carbimazole dose, T4 and TSH levels, attendance dates and several derived variables)from 353 patients, ML models were trained to predict optimal dosing based on prior thyroid function tests and treatment history. Several models outperformed standard physician-guided titration in simulated settings, suggesting potential to enhance biochemical control and reduce over- or undertreatment.

This is one of the many examples of how machine learning may integrate into clinical practice and may improve patient outcomes, also in Endocrinology.

3.12. Graves' disease: latest understanding of pathogenesis and treatment options

Lanzolla G, Marinò M, Menconi F

Nat Rev Endocrinol. 2024 Nov;20(11):647-660.
doi: 10.1038/s41574-024-01016-5. PMID: 39039206

Brief Summary: This narrative review summarizes recent advances in the pathogenesis and treatment of Graves' disease. Drawing on cellular, genetic, and immunological studies, it highlights the central role of autoreactive T and B cells, TSH receptor antibodies and,most importantly, immune tolerance failure. Novel therapeutic approaches targeting these pathways (including monoclonal antibodies and small molecules) are under investigation, not only in mouse models, but also in phase I clinical trials. The review outlines promising directions for individualized and immune-modulating therapies.

Currently, initial treatment of pediatric Graves' disease is medical: anti-thyroid drug(s) (ATD). When this fails or is not possible, definitive treatment should be considered: radioactive iodine or total thyroidectomy [1]. Although longer ATD treatment probably increases the chance of permanent immunological and biochemical remission to 40-50%, more than half of pediatric patient require thyroid gland destruction or removal and, with that, lifelong thyroxine treatment. Novel therapeutic approaches to further improve the chance of permanent immunological remission are needed.

Reference

1. Mooij CF, Cheetham TD, Verburg FA, Eckstein A, Pearce SH, Léger J, van Trotsenburg ASP. 2022 European Thyroid Association Guideline for the management of pediatric Graves' disease. Eur Thyroid J. 2022 Jan 1;11(1):e210073. doi: 10.1530/ETJ-21-0073.21212. PMID: 34981748.

Thyroid Cancer

3.13. Pediatric papillary thyroid carcinoma: outcomes after surgery without adjuvant radioactive iodine

Castellanos LE, Zafereo ME, Sturgis EM, Wang JR, Ying AK, Waguespack SG
J Clin Endocrinol Metab. 2025 Jan 21;110(2):e208-e217.
doi: 10.1210/clinem/dgae576. PMID: 39163248

Brief Summary: This ambispective (i.e. both prospective and retrospective) multicenter study evaluated disease outcomes in pediatric patients <19 years old with papillary thyroid carcinoma (PTC) treated with surgery alone (total thyroidectomy $\pm$ neck dissection, lobectomy $\pm$ neck dissection, or a Sistrunk procedure for ectopic PTC), without adjuvant radioactive iodine (RAI). Among 93 patients (median age 16 years) diagnosed between January 1990 and December 2021 in a tertiary cancer center, most had intermediate-risk disease. After a median follow-up of 5.5 years, most patients (85/93; 91%)remained disease-free, with no disease-related deaths. Only 6 patients (6,5%) required additional therapy (additional surgery or RAI).

These findings suggest that selected pediatric PTC patients can achieve excellent outcomes with surgery alone, supporting more individualized and conservative treatment strategies to avoid potential long-term RAI-related side effects.

Thyroid imaging

3.14. New reference values for thyroid volume by ultrasound in german children and adolescents from a population-based study

Hirtz R, Thamm R, Kuhnert R, Liesenkötter KP, Thamm M, Grasemann C
J Clin Endocrinol Metab. 2025 Jan 21;110(2):e382-e390.
doi: 10.1210/clinem/dgae194. PMID: 38529838

Brief Summary: This population-based cross-sectional study established new reference values for thyroid volume by ultrasound in German children and adolescents. It included 6,553thyroid-healthy and iodine-sufficient participants older than 6 years, selected from 17,641 children who participated in the German Health Interview and Examination Survey for Children and Adolescents. Thyroid volume, measured during the baseline study between 2003 and 2006, strongly correlated with body surface area (BSA), enabling the creation of age- and BSA-specific percentile charts. Compared to World Health Organization (WHO) 2004 references [1], the new values were found to be significantly lower and better reflect current iodine sufficiency.

A strength of this study is that all children had urinary iodine concentration and serum FT4, TSH and TPO antibodies measured. These new reference values will improve diagnostic accuracy in goiter assessment.

Reference

1. Michael B Zimmermann 1, Sonja Y Hess, Luciano Molinari, Bruno De Benoist, François Delange, Lewis E Braverman, Kenji Fujieda, Yoshiya Ito, Pieter L Jooste, KhairyaMoosa, Elizabeth N Pearce, Eduardo A Pretell, Yoshimasa Shishiba. New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a World Health Organization/Nutrition for Health and Development Iodine Deficiency Study Group Report. Am J Clin Nutr. 2004 Feb;79(2):231-7. doi: 10.1093/ajcn/79.2.231. PMID: 14749228

3.15. Assessing the diagnostic accuracy of TI-RADS in pediatric thyroid nodules: a multi-institutional review

Srivatsa S, Al-Hadidi A, Stanek J, Horvath K, Parsons L, Martinez-Rios C, Hopp A, Engle S, Plunk M, Shapira-Zaltsberg G, Nagar S, Masters S, Al-Katib S, Tucker R, AAtweh L, Shah S, Bobbey A, Hoffman R, Aldrink JH
J Pediatr Surg. 2025 Jan;60(1):161924.
doi: 10.1016/j.jpedsurg.2024.161924. PMID: 39358076

Brief Summary: This retrospective multi-institutional study assessed the diagnostic performance of the adult validated American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS) system,and a novel developed and tested pediatric (PED) TI-RADS,compared to American Thyroid Association (ATA) size criteria alone to predict malignancy in pediatric thyroid nodules [1]. Data on 291 nodules from 260 patients (aged 1.3 to 21 years) across 4 institutions were analyzed. Fine-needle aspiration biopsy (FNAB) was performed on 236 nodules, and 99 patients underwent surgical resection with subsequent pathological diagnosis. 46 of these 99 (46.5%) patients had malignancy on the surgical pathology report, giving an overall malignancy rate of 17.7%.

Analyses of sensitivity, specificity, accuracy, and positive/negative predictive of the ACR TI-RADS and the novel PED TI-RADS (with smaller thyroid nodule diameters than used for ACR TI-RADS: FNAB for nodules with a ACR TI-RADS 3 $>$1.5 cm, TI-RADS 4 $>$1.0 cm, and TI-RADS 5 any feasible size)to predict malignancy showed that,with respect to sensitivity (100%),they outperformed previous ATA nodule size criteria when using malignancy on surgical pathology as the true positive. The PED TI-RADS prevented more unnecessary FNAB than using ATA criteria.

Another study in 2024, by Ortega et al, published a retrospective evaluation of the ACR TI-RADS to predict malignancy in pediatric thyroid nodules [2]. From that analysis of 96 patients, of whom 50 (52%) had a malignant nodule on surgical pathology, they proposed to modify the TI-RADS withlower nodule size thresholds for FNAB: they suggest FNAB for all TR3 nodules $\geq$1.5 cm, and FNAB for TR4 and TR5 nodules $\geq$0.5 cm.

Interestingly, size criteria differed between the studies by Srivatsa et al and Ortega et al. If a PED TI-RADS is developed for general use, these should be harmonized.

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2. Carlos A Ortega, Jean-Nicolas Gallant, IremKilic, Siddharth Patel, Sheau-Chiann Chen 5, C Burton Wood, Ryan Adams, Fadi Azer, Huiying Wang, Jiancong Liang, Sara H Duffus, Ryan H Belcher, Rochelle F Andreotti, Rekha Krishnasarma, Jennifer E Lim-Dunham, Güliz A Barkan, Fei Ye, Vivian L Weiss. Evaluation and application of American College of Radiology Thyroid Imaging Reporting and Data System for improved malignancy detection in paediatric thyroid nodules. *Cytopathology*. 2024 Nov;35(6):749-756. doi: 10.1111/cyt.13414. PMID: 38946029.

4. Growth and Growth Factors

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Introduction

In this chapter, we discuss diverse aspects of growth disorders, their underlying genetic mechanisms, and the efficacy and clinical management of growth hormone (GH) therapy in children and adolescents. Among the novel insights into the pathophysiology and treatment of short stature, we highlight the comprehensive genetic characterization of children with Silver–Russell syndrome, the identification of a new pathogenetic variant associated with GH insensitivity (QSOX2 deficiency), and the clinical description of GH secretagogue receptor (GHSR) haploinsufficiency. Encouraging results of GH therapy have also been reported in children carrying mutations in *ACAN*, *NPR2*, *GHR*, and *GHSR*. Of potential relevance to clinical practice is the identification of significant clinical predictors of better first-year response to GH treatment in children with idiopathic short stature (ISS).

The growing use of long-acting GH (LAGH) has prompted us to include statements from an international consensus on LAGH formulations, as well as results from the first LAGH trial in short children born small for gestational age (SGA). Emerging long-term data in children with Prader–Willi syndrome (PWS) receiving GH treatment show an impact on thyroid function. Furthermore, an elegant study, using open-circuit indirect calorimetry with a ventilated hood system, demonstrated that GH therapy has no direct effect on resting energy expenditure in this population.

Finally, recent research indicates that both short stature and growth hormone deficiency (GHD) are associated with distinct alterations in brain structure–function coupling in primary sensory regions, potentially affecting cognitive and behavioral outcomes. These findings underscore the importance of early diagnosis and intervention in GHD.

We hope you enjoy reading this multifaceted chapter, which we believe captures several exciting and clinically meaningful advances in the field of growth.

Novel Genetic Insights

4.1. Distinguishing genetic alterations versus (Epi)mutations in silver–russell syndrome and focus on the IGF1R gene

Alessandro Vimercati, Pierpaola Tannorella, Sara Guzzetti, Luciano Calzari, Davide Gentilini, Emanuela Manfredini, Giulia Gori, Rossella Gaudino, Vincenzo Antona, Maria Piccione, Cecilia Daolio, Renata Auricchio, Fabio Sirchia, Antonella Minelli, Elena Rossi, Melissa Bellini, Giacomo Biasucci, Annalisa Russo Raucci, Gabriella Pozzobon, Giuseppa Patti, Flavia Napoli, Lidia Larizza, Mohamad Maghnie, Silvia Russo

J Clin Endocrinol Metab 2025 Mar 17;110(4):e932-e944.

PMID: 39412159 doi: 10.1210/clinem/dgae730

Brief Summary: Silver–Russell Syndrome (SRS) is a rare growth disorder that presents a significant diagnostic challenge: approximately 40% of clinically suspected SRS cases remain without a molecular diagnosis. This study aimed to identify the underlying genetic variants in 132 genetically undiagnosed SRS patients who fulfilled the Netchine–Harbison Clinical Scoring System (NH-CSS) criteria (score ≥ 4) and lacked known (epi)genetic alterations. Using whole-exome and targeted sequencing, the researchers achieved a diagnostic yield of 9.1% in this challenging cohort.

Pathogenic variants were discovered in the major SRS genes (*IGF2*, *PLAG1*, *HMGA2*), accounting for 3% of cases. Notably, the study identified novel missense and in-frame deletion variants in *PLAG1*, whereas only truncating variants had previously been reported.

Similarly, pathogenic variants in the *IGF1R* gene were identified in 3% of patients. These variants are associated with IGF-1 resistance (IGF1RES), which clinically overlaps with SRS. Importantly, 4 previously unreported likely pathogenic missense variants in *IGF1R* were described. Altogether, variants in *IGF2*, *PLAG1*, *HMGA2*, and *IGF1R* explained 3.6% of SRS cases with NH-CSS ≥ 4.

The study also provided valuable genotype–phenotype correlations: body asymmetry was more frequent in (epi)genetic SRS (72% in IC1_LoM cases) compared with genetic SRS (0–25% in *IGF2*, *HMGA2*, *PLAG1*) and *IGF1R* patients (1.5%), highlighting the link between mosaicism and asymmetry. Relative macrocephaly at birth and postnatally was more common in (epi)genetic SRS (79–80% in IC1_LoM) than in genetic SRS (e.g., 20–27% in *IGF1R*). Conversely, postnatal microcephaly was observed more often in genetic SRS and *IGF1R* patients. Familial cases were frequent, especially in *HMGA2* (60%), *PLAG1* (78%), and *IGF1R* (89%) variants, with affected parents often showing incomplete or milder phenotypes.

In conclusion, this study broadens the molecular spectrum of SRS and, given the diagnostic yield and clinical overlap, strongly supports including *IGF1R* sequencing in the SRS diagnostic workflow. Furthermore, it underscores the importance of parental clinical assessment and genetic counselling due to the high prevalence of familial cases, even among parents with subtle or absent clinical features.

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4.2. Loss-of-function *GHSR* variants are associated with short stature and low IGF-I

Lauren D Punt, Sander Kooijman, Noa J. M Mutsters, Kaiming Yue, Daniëlle C. M van der Kaay, Vera van Tellingen, Willie M Bakker-van Waarde, Annemiek M Boot, Erica L. T van den Akker, Anneke A van Boekholt, Kirsten de Groote, Anne R Kruijsen, Nancy H. G, van Nieuwaal-van Maren, M Claire Woltering, Malou Heijligers, Josine C. van der Heyden, Ellen M. N Bannink, Tuula Rinne, Sabine E Hannema, Wouter J de Waal, Lucia C Delemarre, Patrick C. N Rensen, Christiaan de Bruin, Hermine A van Duyvenvoorde, Jenny A Visser, Patric J. D Delhanty, Monique Losekoot, Jan M Wit, Sjoerd D Joustra

J Clin Endocrinol Metab, 2025, 110, e1303–e1314.
doi: 10.1210/clinem/dgaf010 PMID: 39785833

Brief summary: The growth hormone secretagogue receptor (GHSR), encoded by *GHSR*, is expressed on pituitary somatotrophs and enhances growth hormone (GH) secretion through both constitutive activity and stimulation by ghrelin. Although knockout mouse models suggested that heterozygous GHSR loss-of-function reduces GH response to fasting, data from small human case series have remained inconclusive.

This study aimed to define the clinical phenotype of GHSR haploinsufficiency and evaluate the growth response to GH therapy in affected patients. The authors investigated 26 children (aged 4.0–15.1 years) with short stature carrying heterozygous *GHSR* variants. Ten distinct variants were identified, including 6 novel ones. Functional in vitro studies demonstrated that these variants led to partial or complete loss of receptor function, primarily by abolishing its constitutive activity. Clinically, affected patients presented with proportionate short stature

(mean height −2.8 SDS), reduced IGF-I levels (mean −1.6 SDS), normal stimulated GH peaks, and, in some cases, failure to thrive associated with low appetite. Nine patients were treated with recombinant human GH (rhGH), achieving significant height improvements: an average gain of +0.9 SDS after 1 year and +1.5 SDS after 2 years. Two patients reached near-adult height, showing gains of +1.7 to +1.9 SDS from baseline. The study concludes that *GHSR* variants cause short stature through GH neurosecretory dysfunction, as receptor loss-of-function impairs spontaneous GH release despite normal responses in GH stimulation tests. These findings underscore the critical physiological role of GHSR in GH regulation and support rhGH therapy as an effective intervention. Notably, the study also observed incomplete penetrance, with some carriers of pathogenic *GHSR* variants exhibiting normal stature—suggesting the influence of additional genetic or environmental modifiers.

Overall, this work strengthens the concept that pathogenic *GHSR* variants decrease linear growth by impairing both ghrelin-induced and constitutive GH secretion. The authors propose that, beyond rhGH therapy, GH secretagogue receptor agonists might represent a promising therapeutic option in the future. This study thus broadens the molecular spectrum of treatable short stature and highlights the value of genetic testing in children with unexplained growth failure.

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4.3. QSOX2 Deficiency-induced short stature, gastrointestinal dysmotility and immune dysfunction

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Nat Commun. 2024 Sep 28;15(1):8420.

PMID: 39341815. doi: 10.1038/s41467-024-52587-w

Brief Summary: This study identifies and characterizes QSOX2 deficiency, a newly described autosomal recessive multi-system disorder. It investigates the genetic and phenotypic heterogeneity in patients presenting with short stature and other associated symptoms, a significant challenge in pediatric endocrinology where the molecular basis of growth failure often remains unidentified.

Five patients from 3 families presenting with short stature, immune dysfunction, atopic eczema, and gastrointestinal pathology were found to have recessive variants in the *QSOX2* gene. *QSOX2* encodes a nuclear membrane protein involved in disulphide isomerase and oxidoreductase activity. It localizes to the nuclear membrane/nucleoplasm and Golgi apparatus and shares homology with QSOX1, known for protection against oxidative stress. The study reveals that QSOX2 acts as a gatekeeper for regulating the stabilization and import of phosphorylated-STAT5B into the nucleus. STAT5B is a key effector in the GH receptor pathway, crucial for the production of insulin-like growth factor 1 (IGF-1). Loss of QSOX2 function disrupts GH-mediated STAT5B nuclear translocation, this attenuated nuclear localization of STAT5B impairs its transcriptional activities, leading to reduced expression of target genes like IGF-1.

This mechanism explains the observed partial GH insensitivity (GHI) in affected individuals, characterized by consistently low basal IGF-1 levels despite normal GH responses.

A trial of recombinant human GH therapy in 2 probands resulted in modest increases in height and weight SDS and normalized serum IGF-1 levels over 1.5 years. GH therapy did not improve gastrointestinal symptoms. Therapeutic recombinant insulin-like growth factor-1 (rhIGF-1) may be a more effective treatment for this condition.

4.4. The role of IGF1 in determining body composition in children and adolescents with growth hormone deficiency and those with idiopathic short stature

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Endocrine (2024) 86:1110–1120
PMID: 39143422. doi: 10.1007/s12020-024-03992-0

Brief Summary: This observational retrospective study investigated the relationship between insulin-like growth factor-1 (IGF1) levels and body composition in 135 children (64 with Growth Hormone Deficiency (GHD) and 71 with Idiopathic Short Stature (ISS)) undergoing recombinant human growth hormone (rhGH) therapy. 305 bioimpedance analysis (BIA) was used to assess fat percentage (FATP), appendicular skeletal muscle mass (ASMM) z-score, and muscle-to-fat ratio (MFR) z-score.

The main findings regarding the relationship between IGF1 levels and body composition in pediatric patients receiving recombinant human growth hormone (rhGH) treatment are summarized as follows:

- Differences in Body Composition at Baseline: Children with Growth Hormone Deficiency (GHD) showed greater adiposity compared to those with Idiopathic Short Stature (ISS). This was evidenced by higher body mass index (BMI) z-scores, higher fat percentage (FATP), higher truncal FATP, and a lower muscle-to-fat ratio (MFR) z-score in the GHD group. Additionally, the GHD group had higher diastolic blood pressure percentiles. Importantly, the muscle component (appendicular skeletal muscle mass or ASMM z-score) did not differ between the GHD and ISS groups at this initial stage.
- Impact of rhGH Treatment on Body Composition: rhGH treatment appeared to mitigate the initial differences in adiposity between GHD and ISS patients. In rhGH-treated patients, the differences in FATP and truncal FATP between the GHD and ISS groups were no longer significant. Furthermore, rhGH-treated patients in both groups showed lower truncal FATP and higher ASMM z-scores compared to their non-treated counterparts. This suggests that rhGH treatment, by restoring normal IGF1 levels, may promote muscle growth and alleviate the detrimental metabolic impact of increased adiposity.
- Key Factors Influencing Body Composition: higher FATP (adiposity) was associated with female sex and GHD diagnosis.Higher ASMM z-score (muscle mass) was strongly linked to female sex, older age, and higher insulin-like growth factor 1 (IGF1) z-scores. Interestingly, IGF1 z-scores were found to be related to muscle mass but were not associated with adiposity (FATP) or the muscle-to-fat ratio. Neither the socioeconomic position (SEP) index nor the cumulative rhGH dose were significant contributors to any of the body composition parameters in the models. This implies that individual responsiveness to rhGH, mediated by endogenous IGF1 secretion, is a more influential factor for muscle mass than the total dose administered.
- Role of IGF1 Levels: The findings highlight that sex- and age-adjusted IGF1 levels are crucial for determining muscle mass. IGF1 plays a critical role in regulating protein metabolism by enhancing amino acid transport into muscle cells and inhibiting protein degradation, thereby contributing to skeletal muscle preservation and expansion.
- Sex Dimorphism: Female sex was a contributing factor for increased adiposity (higher FATP). However, surprisingly, female sex was also a contributor to a favorable sex- and age-adjusted muscle mass (ASMM z-score) and a better muscle-to-fat ratio z-score. Females also demonstrated a greater increase in IGF1 z-score over time after adjusting for cumulative rhGH dose.

In conclusion, children with GHD are at a higher risk of increased adiposity. The study suggests that rhGH treatment, by restoring normal IGF-1 levels and thereby promoting muscle growth, may help mitigate the adverse metabolic effects associated with this increased adiposity. This highlights the importance of considering both fat and muscle components when managing pediatric patients with GHD. The main strength of the study is its standardized and comprehensive assessment, while a limitation is its cross-sectional design, which precludes causal inferences.

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Important for Clinical Practice

4.5. Clinical predictors of good/poor response to growth hormone treatment in children with idiopathic short stature

Andrew Dauber, Moshe Phillip, Jean-Marc Ferran, Nicky Kelepouris, Navid Nedjatian, Anne Helene Olsen, Alexander Augusto de Lima Jorge

Horm Res Paediatr. 2024 Nov 21:1-12.
PMID: 39571543. doi: 10.1159/000542579

Brief Summary: This study investigated clinical predictors of response to growth hormone treatment (GHT) during the first year in children with Idiopathic Short Stature (ISS). ISS is a heterogeneous condition in which a child is significantly shorter than peers of the same age and sex, without identifiable systemic, endocrine, nutritional, or chromosomal causes, and with normal endogenous GH secretion. While GHT can help some ISS patients to achieve normal adult height, its use remains debated due to variable treatment responses.

The analysis included data from two large observational registries: NordiNet® IOS (NCT00960128) and the ANSWER Program (NCT01009905). The study population comprised 207 prepubertal children aged 3–11 years (boys) and 3–10 years (girls) at treatment initiation. Patients were classified based on their first-year change in height standard deviation score (ΔHSDS): good responders (ΔHSDS > 1.0), middle responders (ΔHSDS 0.4–1.0), and poor responders (ΔHSDS < 0.4). Responsiveness to GH dose was also assessed by annualized ΔHSDS per 10 μg/kg/day GH, categorizing patients into high, medium, and low responsiveness groups.

Younger age at treatment initiation was associated with a higher likelihood of good response (Odds Ratio [OR] 0.69, 95% CI 0.5–0.9; $p = 0.0169$). Good responders had the lowest mean age (6.4 years). Greater distance from target HSDS predicted better response (OR 2.05, 95% CI 1.1–3.9; $p = 0.0259$). Good responders had the largest mean distance from target HSDS (2.3).In univariate analysis, target HSDS (OR 2.66; $p = 0.016$) and maternal HSDS (OR 1.78; $p = 0.058$) were also notable predictors. Neither sex nor average GH dose in the first year independently predicted response in multivariate models. When stratified by responsiveness to GH dose, a positive correlation between GH dose and ΔHSDS was found in the high and medium responsiveness groups ($p = 0.003$ and $p < 0.001$, respectively). Female sex (OR 0.24; $p = 0.042$) was associated with low responsiveness to GH dose, whereas greater distance from target HSDS predicted high responsiveness (OR 1.85; $p = 0.045$).

In conclusion, younger age at treatment start and a greater distance from target HSDS are clinical predictors of better first-year response to GHT in children with ISS. The heterogeneity in GH dose responsiveness suggests underlying individual and possibly genetic differences. Further research into genetic factors may help personalize treatment and improve outcomes.

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4.6. Long-acting growth hormone therapy in pediatric growth hormone deficiency: a consensus statement

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PMID: 39672599. doi: 10.1210/clinem/dgae834

Brief Summary: This consensus statement, developed by an international workgroup of 11 pediatric endocrinology experts from 10 countries, provides practical guidance on the use of long-acting growth hormone (LAGH) therapy for children with GHD. The panel included clinicians and researchers with extensive expertise in daily GH and LAGH therapy, as well as active involvement in related clinical trials and publications.

Once-weekly LAGH formulations (lonapegsomatropin, somapacitan, and somatrogon) have been approved following pivotal phase 3 studies. Their main advantage over daily GH is reduced injection frequency, which may improve adherence and quality of life, particularly as suboptimal adherence to daily GH is common and negatively affects linear growth. Surveys indicate that patients and caregivers strongly prefer LAGH due to lower treatment burden.

Phase 3 trials have shown that LAGHs are noninferior to daily GH in promoting height gain in prepubertal children with GHD. The safety profiles of LAGHs are comparable to daily GH, with no new safety concerns observed during follow-up periods up to five years. Notably, somatrogon was associated with more frequent injection site reactions and pain.

Most children with GHD are eligible for LAGH. Particular benefit may be expected in groups at higher risk of poor adherence—such as adolescents, children with needle phobia or neurodiversity, those living in multiple households, or those who travel frequently.

Dosing and monitoring:

- Dose adjustments are weight-based, similar to daily GH.
- IGF1 levels remain central to treatment monitoring. Samples should be collected ~4 days after somapacitan/somatrogon administration or ~4.5 days after lonapegsomatropin to approximate mean IGF1 exposure.
- The target is an average IGF1 SDS within the normal range (-2 to $+2$, ideally near 0 SDS).
- Direct milligram-to-milligram comparisons between LAGH molecules are inappropriate because of differing pharmacokinetic and pharmacodynamic properties.
- LAGH therapy offers a more flexible window for delayed dosing ($\pm$2–3 days) compared to daily GH.

Knowledge gaps and research needs: Significant gaps remain in long-term, real-world evidence on adherence, safety, and efficacy, including impacts on adult height, body composition, and cardiometabolic health. Additional data are especially needed for patient subgroups underrepresented in trials: cancer and intracranial tumor survivors, very young children (due to hypoglycemia risk), and those with non-GHD indications such as SGA, ISS, Turner, Noonan, SHOX deficiency, and chronic kidney disease.

Conclusion: The consensus underscores the importance of shared decision-making between clinicians, patients, and caregivers when considering LAGH. Ongoing real-world data collection, through registries like GloBE-Reg, will be critical to refine clinical practice and optimize outcomes.

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4.7. Health-related quality of life and problem behavior after GH cessation in adults born small for gestational age: a 12-year follow-up study

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Brief Summary: This study investigated the long-term health-related quality of life (HRQoL) and problem behavior in adults born small for gestational age (SGA) who were treated with growth hormone (GH) during childhood (SGA-GH), following them for 12 years after GH cessation until around age 30.

The study included 176 SGA-GH adults who had participated in Dutch GH trials for persistent short stature after being born SGA. These individuals were followed at 6 months, 2, 5, and 12 years after GH treatment ceased. At the 12-year follow-up (around age 30), 105 of the initial 176 SGA-GH adults remained. Their HRQoL and problem behavior were compared to three untreated age-matched control groups from a separate study (PROGRAM study): SGA-S: 50 adults born SGA with persistent short stature. SGA-CU: 77 adults born SGA with spontaneous catch-up growth to normal height. AGA: 99 adults born appropriate-for-gestational-age with normal height.

Main Outcome Measures:

- HRQoL was assessed using the TNO-AZL Adults Quality of Life (TAAQoL) questionnaire, which comprises 45 items across 12 subscales covering physical and emotional/social aspects of well-being. Higher scores indicate better HRQoL8.
- Problem behavior was assessed using the Adolescent Behavior Check List (ABCL), a questionnaire with 113 questions on specific problem behaviors, categorizing them into total, externalizing, and internalizing problem behavior, along with 8 subscales. Higher scores indicate more problem behavior.
- Contentment with adult height was assessed by questionnaire.

Over 12 years after GH cessation, HRQoL remained largely stable in SGA-GH adults, with some decline in specific physical and sleep-related aspects. Problem behavior, particularly externalizing, decreased. While SGA-GH adults showed similar HRQoL and problem behavior to untreated short SGA adults, they had lower HRQoL and more problem behavior than AGA adults. This suggests that the differences observed in HRQoL and internalizing problem behavior are more likely attributable to the intrinsic nature of being born SGA rather than the GH treatment itself. Although GH treatment increased adult height, adult height had only a small influence on externalizing problem behavior and no association with HRQoL or internalizing problem behavior in the final adjusted models. Non-height-related factors like chronic physical/mental conditions, lifestyle, fat mass, and education played a greater role in HRQoL and problem behavior.

The study highlights the importance of adequate counselling regarding expectations before GH treatment begins. Despite the noted differences in HRQoL and problem behavior compared to AGA adults, previous research from this group indicates that GH treatment in short SGA children is beneficial and safe, including for metabolic, cardiovascular, and cerebrovascular health up to 12 years after cessation.

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4.8. Somapacitan in children born SGA: 52-week efficacy, safety, and IGF-I response results from the phase 2 REAL5 study

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J Clin Endocrinol Metab, 2025, Vol. 110, Issue 4, Pages 1086–1095.
PMID: 39271158 doi: 10.1210/clinem/dgae616

Brief Summary: The phase 2 REAL5 study investigated the efficacy, safety, and tolerability of somapacitan, a once-weekly long-acting growth hormone (LAGH) derivative, in prepubertal short children born small for gestational age (SGA), comparing it to conventional daily growth hormone (GH) administration. Somapacitan is a reversible albumin-binding GH derivative approved for once-weekly treatment of GH deficiency (GHD) in adults and children, and is being evaluated as a less burdensome treatment option for other indications, including SGA.

REAL5 is a randomized, multicenter, open-label, controlled phase 2 study. It comprises a 26-week main phase, a 26-week extension, and an ongoing 4-year safety extension. A total of 62 GH-treatment-naïve, prepubertal short children born SGA were randomized, with 61 completing 52 weeks of treatment. Patients were randomized in a 1:1:1:1:1 ratio to receive either:

Somapacitan at doses of 0.16, 0.20, or 0.24 mg/kg/week or daily GH (Norditropin®) at doses of 0.035 or 0.067 mg/kg/day.

A sustained dose-dependent growth response was observed for somapacitan after 52 weeks.

Estimated mean HV at week 52 was 8.5, 10.4, and 10.7 cm/year for somapacitan 0.16, 0.20, and 0.24 mg/kg/week, respectively. For daily GH, estimated mean HV was 9.3 and 11.2 cm/year for 0.035 and 0.067 mg/kg/day, respectively. Somapacitan 0.24 mg/kg/week demonstrated similar efficacy to daily GH 0.067 mg/kg/day. Dose-dependent increases in total IGF-I and peak IGF-I bioactivity were observed for both treatments and were similar between comparator groups.

Somapacitan was well-tolerated at all doses, with a safety profile consistent with that of daily GH. Only one mild lipoatrophy injection-site reaction was reported in the somapacitan 0.16 mg/kg/week arm after 52 weeks. High adherence was observed across all treatment arms, with mean adherence rates exceeding 94%.

The study concluded that once-weekly somapacitan provides similar efficacy, safety, and tolerability, as well as comparable bioactive and total IGF-I response, as daily GH (specifically, 0.067 mg/kg/day) in children born SGA after 52 weeks of treatment. The somapacitan 0.24 mg/kg/week dose was selected for the ongoing extension phase of the REAL5 study and for recently initiated randomized controlled phase 3 trials (REAL8, REAL9).

These findings suggest that once-weekly somapacitan could represent a favorable and less burdensome treatment option for short children born SGA, potentially improving adherence and clinical outcomes by reducing the frequency of injections from 365 to 52 per year.

4.9. Patterns of brain structure-function coupling variations related to height and growth hormone in children with short stature

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PMID: 40128591 doi: 10.1038/s41390-025-04003-2

Brief Summary: This study investigated the distinct influences of height and growth hormone (GH) on brain structure-function coupling (SC-FC) in children with short stature. It specifically compared three groups: children with growth hormone deficiency (GHD), children with idiopathic short stature (ISS), and healthy controls (HC).

Substantial evidence indicates that brain gray and white matter volumes peak during childhood through early adolescence, which is crucial for cognitive development. While factors like age and sex are known to influence SC-FC coupling, the role of height remained unclear. Previous research identified brain alterations in children with short stature, but a simultaneous analysis across GHD, ISS, and HC groups to differentiate the effects of height and GH was lacking.

The authors hypothesized that both short stature and GHD would lead to distinct patterns of change in brain SC-FC coupling. They analysed retrospective data collected from children aged 6–12 years, including 71 GHD

cases, 80 ISS cases, and 30 HC subjects. Clinical, behavioral assessments (using the Wechsler Intelligence Scales for Children - WISC-IV), and multimodal brain MRI data (Diffusion Tensor Imaging - DTI and resting-state functional MRI - rs-fMRI) were incorporated.

SC-FC coupling matrices were derived from DTI and rs-fMRI data.

Both short-statured groups (GHD and ISS) displayed lower scores across all behavioral cognition scales (e.g., Full-Scale IQ, Perceptual Reasoning Index, Working Memory Index) compared to HC, with no differences between GHD and ISS. This suggests the impact of height, rather than solely GH, on these outcomes. Both GHD and ISS groups exhibited reduced SC-FC coupling in primary sensory regions, specifically the Visual Network (VIS) and Sensorimotor Network (SMN), compared to HC. No differences were found between the GHD and ISS groups in these areas.

GH's Distinct Influence in GHD: A negative correlation between peak GH levels and SC-FC coupling was observed exclusively in the GHD group. While no direct correlation between height and SC-FC coupling was found in an aggregated analysis across all three groups, the differences observed between HC and the short stature groups (GHD and ISS) still underscore the potential influence of height on brain network coupling.

The study demonstrates that height and GH levels have distinct impacts on brain SC-FC coupling in children with short stature and underscores the importance of early intervention for children with GHD, as reduced SC-FC coupling in primary sensory regions may correlate with cognitive and behavioral outcomes. The study acknowledged limitations, including its retrospective design, constrained sample size (especially for HC), and lack of extensive psychological evaluations. Future longitudinal studies are planned to investigate the effects of age and GH treatment more comprehensively.

New Potential Indications for Growth Hormone Therapy

4.10. A clinical trial of high-dose growth hormone in a patient with a dominant-negative growth hormone receptor mutation

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PMID: 38597155 doi: 10.1210/clinem/dgae244

Brief summary: This paper describes a precision medicine intervention for a patient with severe short stature and growth hormone (GH) resistance.

The patient had a heterozygous dominant-negative variant in the *GHR* gene (c.757del, p.Gln253Argfs*2). This specific variant results in the exclusive production of the extracellular domain of the GH receptor, leading to elevated levels of growth hormone binding protein (GHBP). The elevated GHBP acts as a "sponge", binding to circulating GH and preventing it from effectively reaching functional wild-type receptors on cells, causing GH resistance. The study tested whether extremely high-dose GH could overcome this resistance to normalize insulin-like growth factor (IGF)-1 levels and improve growth.

In this single-patient trial, daily subcutaneous GH was escalated to a maximum dose of 250 µg/kg/day. This high dose was required to achieve the target IGF-1 level (above the mean and below +2 SD for age, sex, and Tanner stage). The treatment resulted in significant improvement: the patient's annualized height velocity was 8.7 cm/year, a notable increase of 3.4 cm/year from his baseline, leading to a 0.81 SD gain in height over 12 months. No adverse events were reported despite the high GH dose. The authors suggest the patient was protected because the underlying resistance meant his body was only exposed to a "normal" amount of GH signaling, as evidenced by his IGF-1 levels remaining within the normal range. This GH high-dose approach was preferred over recombinant IGF-1 treatment due to GH's action through both IGF-1–dependent and IGF-1–independent pathways, fewer side effects, and direct addressing of the underlying pathophysiology.

In conclusion, this precision medicine trial successfully demonstrated that extremely high-dose GH can effectively overcome GH resistance caused by elevated GHBP levels, leading to significant growth improvement in this specific patient.

4.11. Treatment of short stature in aggrecan-deficient patients with recombinant human GH: 3-year response

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PMID: 39502477. doi: 10.1210/jendso/bvae177

Brief Summary: Despite the growing recognition of aggrecan (ACAN) deficiency as a cause of short stature, current evidence on the effectiveness of growth-promoting therapies remains heterogeneous, largely due to variable growth hormone (GH) treatment regimens across published reports.

This prospective, open-label, 3-year study evaluated the efficacy and safety of recombinant human growth hormone (rhGH) in 10 prepubertal children (median age 5.6 years, range 2.4–9.7 years) with heterozygous *ACAN* variants and short stature. Participants received rhGH at an initial dose of 50 μg/kg/day, with adjustments guided by monitored IGF-I levels. Median height standard deviation score (HtSDS) increased by +1.21 (range +0.82 to +1.94; P = 0.002) from a baseline of −2.52 to −1.09 after 3 years. Height velocity increased from a median of 5.2 cm/year at baseline to 8.3 cm/year in the first year, 7.7 cm/year in the second year, and 6.8 cm/year in the third year, consistently above pretreatment rates. Median Predicted adult height (PAH)increased by +6.8 cm over the study period (P = 0.002).

No adverse events attributable to rhGH were reported. Some patients developed or had pre-existing osteochondritis dissecans (OD), a known phenotypic feature of *ACAN* deficiency, but rhGH treatment did not worsen these joint manifestations. Bone age advancement remained stable overall. An increased rate of skeletal maturation was observed in 4girls who entered puberty during follow-up. No changes were noted in body proportionality or bone mineral density.

rhGH therapy appears to be both effective and safe in promoting linear growth in children with *ACAN* deficiency. The findings suggest that earlier initiation of treatment may lead to more favorable outcomes due to a stronger early growth response and a longer prepubertal growth window. Continued longitudinal follow-up is essential to assess final adult height and long-term safety.

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4.12. Clinical characteristics and response to growth hormone treatment in 27 children with heterozygous *NPR2* variants: real-world data

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PMID: 40424589. doi: 10.1210/clinem/dgaf309

Brief Summary: This study evaluated the response to GH treatment in 27 children with heterozygous *NPR2* variants, which encode natriuretic peptide receptor-B (NPR-B), a key regulator of endochondral bone growth. These variants are recognized as an important cause of short stature, often diagnosed as idiopathic short stature (ISS). Most patients (89%) exhibited mild skeletal dysplasia features, most commonly dysmorphic hand findings such as brachydactyly (48%) identified through physical and/or radiological assessment. Careful clinical examination, particularly of the hands, proved valuable in raising suspicion for NPR2-related short stature.

Children with truncating *NPR2* variants had shorter stature (median −3.3 SDS) than those with non-truncating variants (median −2.5 SDS). Variants located in the Kinase Homology Domain (KHD) were also associated with more severe short stature (median −3.2 SDS) relative to variants in other domains (median −2.5 SDS). Prepubertal children (n = 15) showed a median height gain of +1.2 SDS over two years of GH treatment,

whereas pubertal children (n = 12) demonstrated a median height gain of +0.5 SDS. Among 6 pubertal children who reached near-adult height, 5 achieved an improvement in final stature, in some cases surpassing −2 SDS or exceeding the height of their affected parent. GH therapy was generally well tolerated; transient elevations in IGF-1 normalized either spontaneously or after dose adjustment.

This study reinforces that heterozygous pathogenic *NPR2* variants commonly present with subtle skeletal dysplasia features, underlining the diagnostic importance of detailed clinical assessment, especially of the hands. GH treatment produced a meaningful growth response in both prepubertal and pubertal patients, with encouraging improvements in near-adult height. Notably, this research nearly doubles the number of NPR2-deficient children and adolescents with reported GH treatment outcomes, and uniquely includes real-world data on near-adult height. However, findings should be interpreted in light of limitations, including potential selection bias, concomitant treatments, and the inherent difficulty of conducting randomized controlled trials in rare conditions.

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New Findings in Children with Prader-Willi Syndrome

4.13. Thyroid hormone levels in children with Prader–Willi syndrome: a randomized controlled growth hormone trial and 10-year growth hormone study

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PMID: 39049789. doi: 10.1093/ejendo/lvae088

Brief Summary: This study investigated thyroid function during growth hormone (GH) treatment in children with Prader-Willi syndrome (PWS), using data from a 2-year randomized controlled trial (RCT) and a 10-year longitudinal GH study.

GH treatment led to a significant decrease in serum free T4 (FT4) levels and an increase in T3 levels, suggesting increased peripheral conversion of FT4 to T3. This was observed in both the 2-year RCT and the larger 10-year longitudinal study. In contrast, FT4 and T3 levels remained largely unchanged in untreated controls. After the initial changes, FT4 and T3 levels normalized and remained stable within the normal range during long-term GH treatment (between 2 and 10 years) in almost all children with PWS. Regarding TSH levels, TSH SDS generally decreased over the long term but remained within the normal range. True hypothyroidism was very rare in children with PWS. Even when FT4 levels were occasionally low (below -2 SDS), TSH levels were typically normal, and T3 levels were almost always normal. In some cases, thyroxin replacement therapy was initiated based solely on low FT4, but T3 and TSH levels were normal, and subsequent normalization of thyroid hormones occurred upon cessation of thyroxin.

Based on these findings, the authors recommend measuring T3 levels when FT4 is low in children with PWS, especially during the first months of GH treatment, to avoid unnecessary thyroxin replacement.

4.14. Measured resting energy expenditure by indirect calorimetry and energy intake in long-term growth hormone-treated children with PWS

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Horm Res Paediatr 2025;98:164–173
PMID: 38368858. doi: 10.1159/000536466

Brief Summary: This study investigated key aspects of energy balance in children with Prader-Willi syndrome (PWS) receiving long-term growth hormone (GH) treatment in the Dutch PWS Cohort Study.

Previous research reported lower resting energy expenditure (REE) in children with PWS, untreated with GH, primarily attributed to their abnormal body composition, specifically their reduced lean body mass (LBM). This lower metabolic rate, combined with an intense drive for food (hyperphagia), places them at high risk for obesity. While GH treatment improves body composition in children with PWS, there is limited data on the long-term effects of GH treatment on REE and energy intake.

Therefore, this study examined REE (mREE), energy intake, and body composition over an extended period of GH treatment in 52 children with PWS, all confirmed by methylation analysis. They had a mean age of 8.53 years and a median GH-treatment duration of 7 years. REE was measured by open-circuit indirect calorimetry using a ventilated hood system, which is considered the method of choice. Dietary energy intake was calculated from a 3-day dietary record completed by parents. LBM and fat mass (FM) were measured using dual-energy X-ray absorptiometry (DXA) scans. Measured REE was also compared to predicted REE calculated using the Schofield equation, a widely used method based on age, sex, weight, and height. Normal REE was defined as 90% to 110% of the predicted value.

GH-treatment duration was not associated with mREE when corrected for sex, age, height, and pubertal stage. This suggests that long-term GH treatment does not influence mREE directly. LBM was associated with higher mREE, but FM% was not. This aligns with previous studies indicating that LBM is a crucial determinant of REE. When compared to predicted REE using the Schofield equation, only 50% of the children had a normal REE. Specifically, 17.3% had low REE, and 32.7% had high REE. This indicates that predictive equations like Schofield's can either overestimate (by an average of 214 kcal/day for those with decreased REE) or underestimate (by an average of 207 kcal/day for those with elevated REE) mREE. A key finding was that mean energy intake was lower than daily energy requirements (DER) for age- and sex-matched healthy children ($p < 0.001$); this deficit increased with age: not reduced in infants (<3.5 years), 23-36% lower in children aged 3.5-12 years, and 49% lower at age 12-18 years. Despite this lower total energy intake, the macronutrient distribution (carbohydrate, protein, fat) was within the acceptable range.

This study is the first to measure REE, by indirect calorimetry and energy intake, in a large cohort of children with PWS undergoing long-term GH treatment. The findings confirm that mREE in children with PWS increases with age, but long-term GH treatment does not directly influence mREE. The strong association between LBM and mREE underscores the importance of therapies that improve or maintain LBM, such as GH treatment, and also highlights the need to focus on stimulating physical activity to achieve this. For clinical practice, the study emphasizes that relying solely on predictive equations for REE can be inaccurate. Therefore, indirect calorimetry is the best option for precisely determining REE when available, to ensure accurate dietary advice for individual patients.

The authors acknowledge limitations, such as not including an untreated control group (due to ethical considerations given the known benefits of GH treatment) and the potential for underreporting in dietary records. However, it provides valuable insights into the energy metabolism of long-term GH-treated children with PWS, reinforcing the role of LBM in energy expenditure and the necessity of strict dietary control for weight management.

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5. Bone, Growth Plate and Mineral Metabolism

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Advances in Clinical Practice

5.1. Preterm birth and risk of bone fractures during childhood and early adulthood

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Journal of Bone and Mineral Research. 2025, 40(3), 382-395.

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Brief Summary: This Finnish nationwide register-linkage cohort study examined the association between gestational age and the likelihood of experiencing a bone fracture in over 223,000 individuals from birth to almost 30 years of age. Surprisingly, individuals, particularly males, born extremely preterm (before 28 weeks) or very preterm (between 28 and 31 weeks) had a lower risk of bone fractures than those born at full term.

Commentary: This study reports the long-term musculoskeletal health of people born prematurely. Given the well-established link between prematurity and reduced bone mineral density (BMD), one might expect higher fracture rates in preterm individuals. However, the data suggest the opposite: individuals born at the earliest gestations, particularly males, were less likely to sustain fractures by early adulthood. These findings challenge the assumption that lower BMD necessarily equates to a higher fracture risk in young populations.

These findings may be explained in several ways. It has been suggested that children born preterm may be less socially active and exhibit less externalising behaviour or sensation seeking. They may also be less likely to take risks than their counterparts born at or near term. Additionally, parents of children born preterm tend to be more overprotective than parents of children born at term. Furthermore, children born preterm may have motor impairments that affect their ability to engage in physical activities. All of these factors could be a plausible explanation for the above findings. However, certain limitations need to be kept in mind. A lack of information on maternal dietary status, childhood lifestyle, dietary status, breastfeeding, vitamin D supplementation and the growth of the index child during childhood and puberty could all be possible confounding factors. The reliability of gestational age must be considered, as prior to 1987–1990, it was determined by the last menstrual period. This could have led to an underestimation of preterm births. The generalisability of the findings may also be affected by the lack of details regarding prenatal and postnatal treatments at that time, as well as the ethnic homogeneity of the Finnish population. Therefore, the results should be interpreted with caution.

This study adds nuance to our understanding of the long-term skeletal outcomes of preterm birth, inviting further research into the behavioural, environmental and physiological factors that shape fracture risk throughout life.

5.2. Bone mineral density in childhood cancer survivors during and after oncological treatment: A systematic review and meta-analysis

Markarian AM, Taaffe DR, Bettariga F, Luo H, Galvão DA, Wilkie JC, Peddle-McIntyre CJ, Newton RU

Osteoporosis International, 2025. 36(5), 767-777.

https://doi.org/10.1007/s00198-025-07458-5

Brief Summary: This systematic review and meta-analysis examined the bone mineral density (BMD) Z-scores of 4,547 childhood cancer patients and survivors. It found significant reductions in BMD Z-scores at various skeletal sites during treatment for cancer, which continued into survivorship. Hip/femoral neck BMD was more affected than lumbar spine BMD.

Commentary: Bone fragility and reduced BMD are significant long-term health concerns for childhood cancer survivors (CCS). Indeed, previous research has highlighted an elevated risk of fragility fractures in this group. This systematic review synthesises existing evidence using a three-level mixed-effects meta-analysis to examine BMD Z-scores in children undergoing cancer treatment and those who have completed it.

The findings confirm a significant decline in BMD Z-scores during treatment that continues into survivorship, particularly at the hip/femoral neck, a critical weight-bearing site. Identifying age at assessment, time since diagnosis, sex and height as moderators of hip/femoral neck BMD Z-scores provides valuable insight into risk factors. From a clinical perspective, these results emphasise the importance of regularly monitoring BMD in CCS patients and highlight the need for early interventions to mitigate bone loss. The study's focus on hip/femoral neck BMD suggests that this site should be routinely assessed, particularly in children with limited physical activity.

Given these results, future clinical trials should evaluate the efficacy of first-line countermeasures, such as regular physical activity, targeted exercise medicine and nutrition therapy, in preventing and managing bone health decline in this population.

5.3. Presentation and outcome in carriers of pathogenic variants in *SLC34A1* and *SLC34A3* encoding sodium-phosphate transporter NPT 2a and 2c

Brunkhorst M, Brunkhorst L, Martens H, Papizh S, Besouw M, Grasemann C, Turan S, Sikora P, Chromek M, Cornelissen E, Fila M, Lilien M, Allgrove J, Neuhaus TJ, Eltan M, Espinosa L, Schnabel D, Gokce I, González-Rodríguez JD, …Haffner D
Kidney International, 2025. 107(1), 116-129.
https://doi.org/10.1016/j.kint.2024.08.035

Brief Summary: This multicentre retrospective study analysed the clinical, biochemical and genetic data of 113 patients from 90 families with pathogenic variants in the *SLC34A1* or *SLC34A3* genes. The study revealed distinct, yet partially overlapping, phenotypes in biallelic carriers of *SLC34A1* and *SLC34A3*, as well as limited efficacy of phosphate treatment in improving outcomes. Furthermore, the study found an increased risk of chronic kidney disease in adult patients with biallelic *SLC34A3* variants.

Commentary: Phosphate homeostasis is regulated by the renal sodium-phosphate transporters NPT2a (encoded by the *SLC34A1* gene) and NPT2c (encoded by the *SLC34A3* gene). Pathogenic variants in these genes are a rare cause of phosphate wasting. Biallelic variants in *SLC34A1* have historically been associated with infantile hypercalcemia-2 (IH2), whereas biallelic variants in *SLC34A3* cause hereditary hypophosphatemic rickets with hypercalciuria (HHRH). This study represents the largest cohort to date investigating the presentation and long-term outcomes of individuals with pathogenic or likely pathogenic variants in these genes.

This study detailed the distinct phenotypic differences between biallelic *SLC34A1* and *SLC34A3* carriers. *SLC34A1* variant carriers typically present in infancy with symptoms of hypercalcemia (such as polyuria, failure to thrive, vomiting, constipation) and nephrocalcinosis. In contrast, *SLC34A3* variant carriers usually present in childhood or adulthood with hypophosphatemic rickets and less frequent nephrocalcinosis. The study also highlights that adult biallelic *SLC34A3* carriers have a 6-fold increased risk of chronic kidney disease compared to the general population. While both groups share a common biochemical pattern of elevated 1,25(OH)2D and alkaline phosphatase levels, suppressed parathyroid hormone, and hypercalciuria, the study reports that phosphate treatmentonly partially improves clinical and biochemical features and may even lead to increased PTH levels, potentially exacerbating renal phosphate loss. The study also suggests that heterozygous carriers, previously thought to be unaffected, might exhibit milder phenotypes and an increased risk of renal calcification.

5.4. Disease burden by ALPL variant number in patients with non-life-threatening hypophosphatasia in the global HPP registry

Kishnani PS, Seefried L, Dahir KM, Martos-Moreno GÁ, Högler W, Greenberg CR, Fang S, Petryk A, Mowrey WR, Linglart A, &Ozono K

Journal of Medical Genetics, 2025. 62(4), 249-257.

https://doi.org/10.1136/jmg-2024-110383

Brief Summary: This study compared the disease burden in patients with non-life-threatening hypophosphatasia (HPP), based on the number of *ALPL* variants present (one versus two or more). Although patients with 2 or more variants had a higher prevalence of HPP-specific manifestations, their overall patient-reported outcomes for pain, disability and quality of life were similar to those of patients with 1 variant.

Commentary: Hypophosphatasia (HPP) is a rare inherited metabolic disorder characterised by deficient tissue-non-specific alkaline phosphatase (ALP) enzyme activity. This leads to a wide spectrum of clinical manifestations. Although severe, life-threatening forms of HPP that manifest in infancy are well characterised, less is known about the disease burden in patients who develop symptoms after six months of age and who have varying numbers of *ALPL* gene variants. This study analysed data from the Global HPP Registry, focusing on patients with non-life-threatening HPP, in order to understand the relationship between the number of *ALPL* variants and disease burden.

The findings reveal that the disease burden associated with HPP remains high regardless of the number of *ALPL* variants, significantly impacting quality of life, pain, and disability across all patient groups. Patients with 2 or more *ALPL* variants are often diagnosed at a younger age and show a higher prevalence of specific skeletal, dental, muscular and neurological manifestations. However, there was no difference in patient-reported outcomes, such as pain and quality of life, between those with 1 variant and those with 2 or more variants. These results suggest that the clinical status of patients should be the primary consideration for access to effective treatments such as enzyme replacement therapy, rather than the number of *ALPL* variants alone.

5.5. ENPP1 in blood and bone: skeletal and soft tissue diseases induced by ENPP1 deficiency

Ferreira CR, Carpenter TO, Braddock DT

Annual Review of Pathology, (2024). *19*, 507-540.

https://doi.org/10.1146/annurev-pathmechdis-051222-121126

Brief Summary: This retrospective natural history study analysed data from 84 individuals with ENPP1 deficiency in order to characterise the clinical presentation and progression of generalised arterial calcification of infancy (GACI) and autosomal recessive hypophosphataemic rickets type 2 (ARHR2). The study confirmed the high infant mortality rate associated with GACI, identified prenatal anomalies as common and demonstrated that survivors often develop musculoskeletal complications. This highlights the continuous phenotypic spectrum of the disease.

Commentary: ENPP1 deficiency is a rare genetic mineralization disorder characterized by a spectrum of age-related phenotypes, primarily GACI and ARHR2. Previous understanding of this condition was limited due to small studies and varied clinical presentations with short follow-up durations. This study provides the largest retrospective analysis to date, encompassing 84 individuals, thereby offering a more comprehensive understanding of the disease's natural history and clinical evolution.

First, this study reported the onset and cumulative incidence of ENPP1 deficiency's clinical complications, categorized into calcification, cardiovascular, musculoskeletal, and other organ involvement. The study confirmed that GACI and ARHR2 represent a phenotypic continuum rather than distinct diseases, with many GACI survivors later developing ARHR2. A significant majority (76%) of affected individuals presented in infancy with severe cardiovascular issues and respiratory distress, often requiring acute inpatient care, and noted a high infant mortality rate of 44% in GACI cases. Another finding is the high prevalence of prenatal ultrasound anomalies, such as polyhydramnios and hydrops fetalis, in GACI patients, suggesting the possibility of early

diagnosis. For survivors, musculoskeletal complications, particularly rickets, were common, affecting an estimated 70% of individuals by age 10. This study also sheds light on the variable clinical presentation, even among siblings, and the challenges in diagnosis due to the overlap of symptoms with other conditions, such as FGF23-related hypophosphatemic rickets.

5.6. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia

Haffner D, Emma F, Seefried L, Högler W, Javaid, KM, Bockenhauer D, Bacchetta J, Eastwood D, BiosseDuplan M, Schnabel D, Wicart P, Ariceta G, Levtchenko E, Harvengt P, Kirchhoff M, Gardiner O, Di Rocco F, Chaussain C, Brandi ML, Linglart A
Nature Reviews. Nephrology, (2025). *21*(5), 330-354.
https://doi.org/10.1038/s41581-024-00926-x

Brief Summary: This paper provides updated clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia (XLH), based on a comprehensive literature review and expert consensus.

Commentary: X-linked hypophosphataemia (XLH) is a rare genetic metabolic bone disorder primarily caused by pathogenic variants in *PHEX*. This leads to increased levels of fibroblast growth factor 23 (FGF23). The resulting excess FGF23 causes renal phosphate wasting and a range of debilitating symptoms, including rickets, osteomalacia, bone pain and dental issues. Historically, treatment involved frequent doses of oral phosphate supplements and active vitamin D, which were only partially effective and had significant side effects, including hyperparathyroidism and nephrocalcinosis.

XLH management has evolved significantly with the development of burosumab, a humanised monoclonal antibody that neutralises circulating FGF23. This study provides updated, evidence-based clinical practice recommendations reflecting the latest treatment advancements, particularly the widespread availability of burosumab since 2018. The main advance highlighted is the shift towards using burosumab as the primary treatment for children with symptoms, due to its superior ability to normalise phosphate levels, improve rickets and reduce associated complications. For adults, it is recommended for individuals with pseudofractures, an inadequate response to conventional therapy, or significant adverse effects from traditional treatments. This study also offers guidance on the diagnosis, monitoring and management of various XLH manifestations across different age groups, as well as considerations for specific situations such as pregnancy and orthopaedic interventions.

Novel Treatments

5.7. Evaluation of the benefits of adapted physical activity in children and adolescents with osteogenesis imperfecta: the MOVE-OI trial

Al Arab H, Flammier S, Espitalier M, Bacchetta J, Fouillet-Desjonqueres M
Orphanet Journal of Rare Diseases, (2025). 20(1), 175.
https://doi.org/10.1186/s13023-025-03678-4

Brief Summary: This prospective, single-centre study evaluated the impact of a 12-month, individually-adapted physical activity programme on 30 children and adolescents with osteogenesis imperfecta (OI). The study demonstrated an improvement of 17% in the 6-minute walk test (6 MWT) distance, alongside a reduction in fracture incidence and an improvement in quality of life for those with high baseline difficulty.

Commentary: Osteogenesis imperfecta (OI) is a rare genetic disorder characterised by bone fragility and an increased susceptibility to fractures. While current treatments primarily focus on reducing fracture incidence and

improving quality of life, the role of physical activity in managing OI remains under-explored. This study investigates the benefits of adapted physical activity (APA) for paediatric patients with OI.

The main findings include a 17% increase in 6MWT distance, indicating improved physical capacity and endurance, as well as a reduction in fracture incidence from 40% to 20%. Additionally, quality of life improved for participants who initially reported greater difficulty. While previous studies have demonstrated improvements in the physical capacity of patients with OI, the current findings are notable as they show the feasibility and advantages of a home-based APA programme. This offers a more accessible and sustainable approach, which is particularly important when access to specialised rehabilitation centres is limited. The study design involved regular contact with an APA instructor and comprehensive assessments to ensure adherence and monitoring.

This study highlights the need to integrate tailored APA programmes into the routine clinical management of children with OI, enhancing long-term outcomes and supporting their overall well-being.

5.8. Severity of acute phase reaction in children receiving the first dose of zoledronic acid and the impact of the underlying condition: a cross-sectional study

Nayak S, Rayner L, Mughal Z, McKinney G, Mason A, Wong S.C, Padidela R, Chinoy A
Archives of Disease in Childhood, (2024). 109(10), 849-853.
https://doi.org/10.1136/archdischild-2023-326287

Brief Summary: This retrospective cross-sectional study examined the severity of the acute phase reaction (APR) experienced by 107 children following their first zoledronate infusion. Most patients experienced a mild APR that did not require overnight hospital admission; however, certain patient groups exhibited more severe reactions.

Commentary: Zoledronate, a widely used bisphosphonate for treating osteoporosis in children, is known to cause an acute phase reaction after the initial dose. This often leads to routine overnight hospital admissions for monitoring. While this approach is cautious, it contributes to significant healthcare costs and resource utilisation. This study addresses this issue by providing objective evidence on the severity of the APR, with the aim of informing more selective admission policies.

The study demonstrates that the APR is usually mild, enabling outpatient management in most cases and improving both resource allocation and patient experience. However, the study also identifies specific 'high-risk' patient categories who may still benefit from inpatient monitoring due to more severe reactions, such as those with Duchenne muscular dystrophy, systemic inflammatory disorders/steroid-induced osteoporosis, and epilepsy. These findings enable a more individualised approach of patients treated with bisphosphonates.

5.9. Early and multiple doses of zoledronate mitigates rebound bone loss following withdrawal of receptor activator of nuclear factor kappa-B ligand inhibition

Kim AS, Taylor VE, Castro-Martinez A, Dhakal S, Zamerli A, Mohanty ST, Xiao Y, Simic MK, Pantalone A, Chu J, Cheng TL, Croucher PI, Center JR, Girgis CM, McDonald MM
Journal of Bone and Mineral Research, (2025). 40(3), 413-427.
https://doi.org/10.1093/jbmr/zjaf008

Brief Summary: This mouse model study investigated strategies for the sequential administration of zoledronate following the withdrawal of denosumab. Administration of multiple doses of zoledronate at an early stage mitigated the rebound of bone loss, improves bone microarchitecture, and increases fracture resistance.

Commentary: Denosumab is a humanised monoclonal antibody that inhibits RANKL with potent anti-osteoclastic effects. However, it presents a significant clinical challenge upon discontinuation due to rapid and

severe rebound bone loss, which often leads to an increased risk of fractures. This study investigated the effect of an earlier, multi-dose zoledronate intervention strategy. Preclinical data have revealed that the processes driving rebound bone loss, particularly the increase in osteoclast activity (as indicated by serum TRAP levels), occur at an earlier stage than previously recognised clinical markers such as the rise in CTX levels or the loss of BMD. This provides a crucial 'earlier intervention window'.

This study demonstrates that, when administered early (before detectable bone loss) and in multiple doses, zoledronate can successfully prevent overshooting osteoclast activity and consolidate the gains in bone mineral density achieved with denosumab. These findings were validated in both young, growing mice and older, skeletally mature mice, enhancing their potential for translation to diverse patient populations. Furthermore, this early, multi-dose approach preserves bone density and improves trabecular and cortical bone microarchitecture, thereby increasing fracture resistance in skeletally mature mice. These findings could be used to improve the management of patients who are discontinuing denosumab treatment.

5.10. Achondroplasia: aligning mouse model with human clinical studies shows crucial importance of immediate postnatal start of the therapy

Rico-Llanos G, Spoutil F, Blahova E, Koudelka A, Prochazkova M, Czyrek A, Fafilek B, Prochazka J, Gonzalez Lopez M, Krivanek J, Sedlacek R, Krakow D, Nonaka Y, Nakamura Y, Krejci P
Journal of Bone and Mineral Research, (2024). 39(12), 1783-1792.
https://doi.org/10.1093/jbmr/zjae173

Brief Summary: This study used a mouse model of achondroplasia to compare the efficacy of early versus late postnatal treatment with the FGFR3 inhibitor,infigratinib. It demonstrated that early intervention is crucial for restoring cranial base development and preventing associated neurological complications. Both early and late treatments improved long bone growth.

Commentary: Achondroplasia (ACH) is the most common form of human dwarfism and is caused by mutations in the FGFR3 receptor. Current therapies, such as C-natriuretic peptide (CNP) analogues and tyrosine kinase inhibitors, mainly aim to increase longitudinal growth. However, they often fail to address early cranial malformationssuch as midface hypoplasia and foramen magnum stenosis. These malformations can lead to significant otolaryngeal and neurological issues, including obstructive sleep apnoea and sudden infant death syndrome. Using a mouse model that recapitulates human ACH pathology, this study compared the effects of treatment initiated immediately after birth (day 1) and later postnatal treatment (day 4, equivalent to ~5 months in humans) with infigratinib, a tyrosine kinase inhibitor.

This study demonstrates that immediate postnatal therapy is essential for normalising skeletal growth in the cranial base and long bones. Specifically, early treatment improved naso-anal length and vertebral growth. Importantly, it also restored defective cranial development, including the fronto-basal angle and the area of the foramen magnum. In contrast, late treatment provided little to no improvement for cranial malformations, although it did promote long bone growth in a similar manner to early treatment. The study also revealed that premature fusion of skull base synchondroses occurs immediately after birth in achondroplasia, resulting in defective cranial development.

These results suggest that children with achondroplasia should receive treatment as early as possible to prevent complications during the early years of life.

5.11. Oral infigratinib therapy in children with achondroplasia

Savarirayan R, De Bergua JM, Arundel P, Salles JP, Saraff V, Delgado B, Leiva-Gea A, McDevitt H, Nicolino M, Rossi M, Salcedo M, Cormier-Daire V, Skae M, Kannu P, Phillips J, Saal H, Harmatz P, Candler T, Hill D, Rogoff D
The New England Journal of Medicine. 2025.392(9):865-874. PMID: 39555818
https://doi.org/10.1056/NEJMoa2411790

Brief Summary: This Phase 2 dose-finding study evaluated the safety and efficacy of oral infigratinib in children aged 3 to 11 with achondroplasia. Infigratinib was generally well tolerated and that, at the highest dose, it increased annualised height velocity and improved body proportions over 18 months.

Commentary: Achondroplasia, the most common form of disproportionate short stature, is caused by gain-of-function pathogenic variants in the *FGFR3* gene. This leads to impaired endochondral ossification and various medical complications. Infigratinib is an orally bioavailable, selective tyrosine kinase inhibitor of FGFR1-3 that directly targets the underlying pathophysiological mechanism by inhibiting FGFR phosphorylation and attenuating downstream signalling pathways.

This study shows that infigratinib is well tolerated orally, with mostly mild or moderate adverse events that did not lead to treatment discontinuation, and that it effectively promotes linear growth. Specifically, the highest dose (0.25 mg per kilogram) led to a sustained increase in annualised height velocity (mean change from baseline at 18 months: 2.5 cm per year) and a decrease in the upper-to-lower body segment ratio, thereby addressing the characteristic disproportion in achondroplasia. This is particularly noteworthy given that previous oncology studies used much higher doses; this study confirms the efficacy of significantly lower, safer levels for children. The positive results of this phase 2 study, particularly with regard to efficacy and the safety profile, must be confirmed in a phase 3 trial in order to evaluate infigratinib further in a larger cohort of children.

Various therapeutic trials are currently being evaluated in achondroplasia (vosoritide, TransCon CNP, infigratinib). It will be important to determine the relative efficacy of these different treatments in the future, and also to evaluate therapies combining these compounds.

5.12. Palovarotene (Sohonos), a synthetic retinoid for reducing new heterotopic ossification in fibrodysplasia ossificans progressiva: history, present, and future.

Hsiao EC, Pacifici M
JBMR Plus, (2025). 9(1), ziae147.
https://doi.org/10.1093/jbmrpl/ziae147

Brief Summary: This review outlines the development of palovarotene (Sohonos), a selective retinoic acid receptor (RAR) agonist, as a potential treatment for fibrodysplasia ossificans progressiva (FOP), a rare and debilitating genetic condition characterised by progressive heterotopic ossification (HO). It outlines the drug's mechanism of action and the rationale behind its use in preclinical studies. It also summarises the findings of clinical trials, including data from the pivotal Phase 3 MOVE trial, which ultimately supported the drug's regulatory approval in the United States.

Commentary: This review describes how the study of retinoid signalling biology led to a real-world treatment. The drug's targeted inhibition of chondrogenesis and downstream ossification processes, hallmarks of HO in FOP, makes it a uniquely mechanism-based therapy. By modulating SMAD signalling and suppressing progenitor cell recruitment, palovarotene directly interferes with the ectopic skeletal cascade that defines the disease.

Palovarotene was investigated as a potential therapy to reduce heterotopic ossification (HO) in FOP. Despite the absence of a statistically significant effect in Phase 2 studies, a Phase 3 MOVE trial of palovarotene was conducted. This single-arm, open-label study compared patients treated with palovarotene with natural history controls. Subjects aged 4+ years were treated with either a daily dose or a flare-up dose of palovarotene. Annualised change in new HO formation was assessed using low-dose CT scans. The data from the MOVE trial were then compared with those from the FOP Natural History Study (NHS). Although the primary analysis was complicated by limitations in the statistical model and discrepancies in the imaging schedule, post hoc analyses indicated a 60% reduction in new HO volume. Notably, a matched-pair analysis revealed a reduction in HO formation among patients who transitioned from the natural history cohort to palovarotene treatment. These findings were pivotal in securing FDA approval in 2023.

However, this treatment has also been linked to serious adverse events, prompting the European Medicines Agency to reject it. Notably, 21 out of 57 children under the age of 14 experienced premature physeal closure

(PPC), resulting in a partial clinical hold and age-related prescribing restrictions. People with FOP may already have reduced bone density, increasing the risk of osteoporosis-related fractures at a young age. Palovarotene may also interfere with fracture healing by inhibiting osteogenesis.

Further clinical trials are needed to clarify the efficacy and safety of palovarotene treatment in patients with FOP.

Advances in Growth, Bone Biology and Mineral Metabolism

5.13. The Ip6k1 and Ip6k2 kinases are critical for normal renal tubular function

Haykir B, Moser SO, Pastor-Arroyo EM, Schnitzbauer U, Radvanyi Z, Prucker I, Qiu D, Fiedler D, Saiardi A, Jessen HJ, Hernando N, Wagner CA

Journal of the American Society of Nephrology. (2024). 35(4), 441-455.

https://doi.org/10.1681/ASN.0000000000000303

Brief Summary: This study used both *in vitro* opossum kidney cells and *in vivo* renal tubular-specific IP6K1/2 knockout mice to investigate the role of IP6K1/2 kinases in phosphate homeostasis. Depleting these kinases impaired phosphate transport and disrupted other kidney functions, particularly in males.

Commentary: Inorganic phosphate is an essential mineral whose tightly controlled plasma levels are crucial for various biological processes, including the formation of cellular membranes, DNA and RNA, and bones. Dysregulation can lead to severe health issues such as hyperphosphatemia, which is associated with cardiovascular disease, or hypophosphatemia, which affects bone. The kidneys play a central role in maintaining this balance by regulating phosphate reabsorption, primarily through Na/Pi cotransporters such as NaPi-IIa and NaPi-IIc in the proximal tubules. Although 5-IP7, an inositol pyrophosphate generated by IP6Ks, is known to regulate phosphate metabolism in yeast and plants, its role in mammalian phosphate homeostasis remains largely unexplored.

This study demonstrates that IP6K1 and IP6K2 are essential for the normal functioning of the renal tubule in mammals. Depletion of these kinases in both *in vitro* and *in vivo* models was found to lead to reduced phosphate transport and altered expression of key Na+/Pi cotransporters. Specifically, male IP6K1/2 knockout mice developed hypophosphataemia, increased bone resorption and general tubular dysfunction, including increased diuresis, albuminuria and hypercalciuria. These findings highlight the essential role of IP6Ks in not only phosphate metabolism, but also broader kidney functions, suggesting a more complex role than previously thought. However, these findings also suggest that, while pharmacological inhibition of these kinases could potentially target phosphate metabolism, it could lead to severe and undesirable side effects due to their broader impact on kidney function.

Further research is needed to clarify the therapeutic potential and safety considerations of targeting IP6K pathways for phosphate-related disorders.

5.14. miRNA-based regulation in growth plate cartilage: mechanisms, targets, and therapeutic potential

Thakore P, Delany AM

Frontiers in Endocrinology, (2025). 16, 1530374.

https://doi.org/10.3389/fendo.2025.1530374

Brief Summary:This review explores the critical role of microRNAs (miRNAs) in regulating gene expression within the growth plate, which is a key structure for longitudinal bone growth. It discusses the mechanisms by which miRNAs such as miR-140, miR-1 and miR-26b influence the proliferation, differentiation and hypertrophy of chondrocytes, and emphasises their potential for use in the treatment of skeletal disorders such as idiopathic short stature and physeal injuries. The article emphasises recent advances in miRNA-based therapeutics and delivery systems, suggesting promising avenues for targeted skeletal repair.

Commentary: This review sheds light on the role of microRNAs (miRNAs) in modulating growth plate dynamics, which are fundamental to paediatric skeletal development. The authors chart how miRNAs such as miR-140, miR-1 and miR-26b act as molecular rheostats, fine-tuning gene expression during chondrocyte maturation and influencing key pathways such as PTHrP-IHH, BMP and WNT signalling. The clinical implications are significant: miR-140 mutations have been linked to human skeletal dysplasia, while miR-26b-3p is emerging as a potential biomarker and therapeutic target in idiopathic short stature. The review also highlights the development of miRNA-based therapies that could be used to prevent or repair physeal bony bridge formation, a challenging paediatric complication. The discussion of delivery challenges in dense, avascular cartilage and innovations such as cartilage-penetrating nanoparticles and exosome-based systems provides a realistic perspective on the therapeutic potential.

6. DSD and Gender Incongruence

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Preface

In the past 12 months, between June 2024 and July 2025, the search for "Differences of Sexual Development" or "disorders of sex development" or "ambiguous genitalia" or "gonadal development" or "DSD" and "gender incongruence" or "gender dysphoria" in PubMed yielded more than 1000 publications published in English.

Among those, 18 are summarized in this chapter. The selection process was very challenging given the space available, but we prioritized the key publications chosen on the quality of methodology, the significance of the outcome, and particularly the impact on clinical practice. We have endeavored to balance basic research and clinical articles.

This year's selected articles on disorders of sex development (DSD) covers topics such as 1. Recent information about nuclear receptor genes associated with sexual development, 2. New insights about the X chromosome in men and women, 3. Various aspects of testicular/ovotesticular DSD and, 4. DSD associated with Rare Mitochondrial Disorders. The selection of gender incongruence articles presents new clinical insights on the effects of the use of GnRH analogue and/orsex hormone treatment on the 1. immune system, 2. renal function, 3. sexual functioning in transgender individuals and briefly discusses opportunities and threats for transgender care.

We hope these selected publications will help to increase understanding and improve clinical care of patients.

DSD Papers: Recent Information about Nuclear Receptor Genes Associated with Sexual Development

6.1. Oligogenic analysis across broad phenotypes of 46,XY differences in sex development associated with NR5A1/SF-1 variants: findings from the international SF1next study

Kouri C, Martinez de Lapiscina I, Naamneh-Elzenaty R, Sommer G, Sauter KS, Flück CE; SF1next study group
EBioMedicine. 2025 Mar;113:105624.
doi: 10.1016/j.ebiom.2025.105624

Brief summary: This study examined 30 individuals with 46,XY DSD carrying *NR5A1/SF-1* variants and finds that co-existing variants in other DSD-related genes may explain their diverse phenotypic variability. The findings support an oligogenic rather than monogenic model of DSD. This has important implications for diagnosis, genetic counseling, and management.

Despite >100 genes being linked to DSD, nearly half of all DSD patients still lack a clear genetic diagnosis. While standard testing methods typically identify coding SNVs and CNVs, other contributors, such as intronic variants, mosaicism, structural or epigenetic alterations, and oligogenic inheritance, may go undetected. Next-generation sequencing (NGS) has enabled the identification of oligogenic causes in endocrine disorders,

including DSD. Among these, *NR5A1/SF-1* variants stand out for their highly variable phenotypes, ranging from severe DSD to isolated infertility or even asymptomatic individuals. Although several mechanisms have been proposed to explain this variability, including haploinsufficiency and dominant-negative effects, none have been conclusively proven. The recent international SF1next study, involving 197 individuals with *NR5A1/SF-1* variants, the largest such cohort to date, found no clear genotype–phenotype correlation (1). However, it revealed a higher prevalence of associated anomalies, especially affecting the spleen, and noted that severe DSD cases frequently showed atypical puberty and predicted fertility issues. These observations support oligogenic inheritance as a likely explanation. To explore this, Kouri *et al*. conducted whole exome sequencing (WES) on family trios and applied disease-specific bioinformatic tools. Their findings identified additional variants in genes like *TBCE, FLNB, GLI3, PDGFRA*, and others frequently associated with DSD (e.g., *CDH23, GLI2, KAT6B, MYO7A, PKD1, SPRY4, ZFPM2*), suggesting multilocus contributions to the DSD phenotype.

This study underscores the need for advanced genetic testing and bioinformatic analyses using disease-specific algorithms to comprehensively identify and interpret the full spectrum of genetic variants involved in DSD. The complexity of DSD associated with NR5A1/SF-1 variants suggests the involvement of additional genetic factors, highlighting the importance of further research into potential multilocus contributions.

Reference

1. Kouri C, Sommer G, Martinez de Lapiscina I, Elzenaty RN, Tack LJW, Cools M, Ahmed SF, Flück CE; SF1next study group. Clinical and genetic characteristics of a large international cohort of individuals with rare NR5A1/SF-1 variants of sex development. EBioMedicine. 2024 Jan;99:104941. PMID: 38168586.

6.2. Identification, structure, and agonist design of an androgen membrane receptor

Yang Z, Ping YQ, Wang MW, Zhang C, Zhou SH, Xi YT, Zhu KK, Ding W, Zhang QY, Song ZC, Zhao RJ, He ZL, Wang MX, Qi L, Ullmann C, Ricken A, Schöneberg T, Gan ZJ, Yu X, Xiao P, Yi F, Liebscher I, Sun JP

Cell. 2025 Mar 20;188(6):1589-1604.e24.

doi: 10.1016/j.cell.2025.01.006

Brief summary: This study identified GPR133, an adhesion type G protein coupled receptor, as a functional membrane receptor for the androgen 5α-dihydrotestosterone (5α-DHT). When activated by 5α-DHT in muscle cells, GPR133 increases intracellular cAMP levels, improving muscle strength. Cryo-electron microscopy elucidated the structural basis of steroid recognition by GPR133, revealing key motifs ("$\Phi(F/l)^{2.64}$–$F^{3.40}$–$W^{6.53}$" and "$F^{7.42}\times\times N/D^{7.46}$") within adhesion G protein-coupled receptors (GPCRs) that bind the hydrophobic steroid core and polar groups.

Further, the authors used computational screening to design AP503, a selective small-molecule agonist for GPR133. AP503 replicated the muscle-strengthening benefits of androgens without the typical side effects mediated by nuclear androgen receptors. This work positions GPR133 as a novel therapeutic target for enhancing skeletal muscle function.

Traditionally, the effects of androgens were thought to be mediated almost exclusively through nuclear androgen receptors (ARs). However, the rapid actions of 5α-DHT, unexplained by genomic mechanisms, suggest the existence of alternative signaling pathways. This work convincingly establishes GPR133 as a functional GPCR that mediates fast androgen responses and promotes muscle strength via PKA-dependent phosphorylation cascades.

The structural elucidation of GPR133 in complex with 5α-DHT in both high- and low-affinity binding states adds depth to our understanding of steroid-GPCR interactions. The physiological relevance of GPR133 in skeletal muscle function is well-demonstrated, with downstream signaling traced through *MLCK2* and *RYR1* activation, as well as the development of a synthetic agonist (AP503) that mimics androgen effects without activating AR.

AP503 represents a promising pharmacological tool that could bypass the side effects of traditional anabolic steroids. Its specificity for GPR133, sparing the AR, is particularly important for developing safer therapies targeting muscle weakness or sarcopenia. However, while the study identifies GPR133 as a key membrane receptor for 5α-DHT, the muscle-strengthening effect was not completely abolished in *Gpr133* knockout mice. This strongly suggests the involvement of other yet unidentified, membrane receptors or compensatory

pathways. A comprehensive mapping of potential additional GPCRs responsive to androgens is warranted. Furthermore, although AP503 showed efficacy in muscle strength enhancement in preclinical models, its safety, efficacy, and long-term impact in clinically relevant modelsremain unexplored, particularly aging or disease states like sarcopenia. Future studies are crucial for evaluating the translational potential of this compound. However, the findings lay an important foundation for the development of next-generation androgenic therapies with reduced adverse effects.

6.3. NR2F2 regulation of interstitial cell fate in the embryonic mouse testis and its impact on differences of sex development

Estermann MA, Grimm SA, Kitakule AS, Rodriguez KF, Brown PR, McClelland K, Amato CM, Yao HH
Nat Commun. 2025 Apr 29;16(1):3987.
doi: 10.1038/s41467-025-59183-6

Brief summary: This study combined single-nucleus multiomics, ChIP-seq and genetic mouse models, Estermann and collagues investigated the role of *NR2F2*, an orphan nuclear receptor, in shaping the fate of interstitial cells during embryonic testis development in mice. Their findings demonstrate that *NR2F2* is crucial for guiding progenitor cells toward steroidogenic Leydig cell lineage rather than other interstitial cell types. Genetic deletion of *NR2F2* disrupts Leydig cell differentiation, leading to abnormal Sertoli–Leydig cell balance, impaired androgen production, and disruption in testis architecture. These developmental perturbations provide a mechanistic link between NR2F2 dysfunction and DSD, underscoring its significance in ensuring proper sex differentiation via endocrine pathways.

This study provides important insights into fetal Leydig cell biology by highlighting the often-overlooked role of the interstitial compartment of the embryonic testis, particularly the transcription factor NR2F2 (COUP-TFII). While testicular development research has largely focused on Sertoli and germ cells, this work emphasizes the diversity of non-steroidogenic interstitial cells and their impact on testicular architecture and male sex development.

Fetal Leydig cells emerge from interstitial progenitors around embryonic day 12.5 in mice. Their differentiation is promoted by Desert Hedgehog (DHH) signaling and inhibited by Notch and VEGF pathways. Disruptions in this balance may result in DSD and male reproductive defects. The interstitial space also contains other non-steroidogenic cells marked by genes such as *Tcf21*, *Wnt5a*, *Arx*, *Pdgfra*, and *Nr2f2*. These markers contribute to specific lineages, including Leydig and peritubular myoid cells.

Using multi-omics and genetic mouse models, the authors identify fetal Leydig progenitors and demonstrate that NR2F2 is essential for their differentiation from non-steroidogenic interstitial cells. NR2F2 regulates interstitial cell identity and inhibits premature Leydig differentiation by repressing Notch/VEGF signaling and key steroidogenic genes. Loss of Nr2f2 leads to phenotypes resembling human DSD, including gonadal dysgenesis, cryptorchidism, hypospadias, and Leydig cell hypoplasia.

Despite its strengths, the study has limitations. The lack of lineage tracing before E11.5 leaves the earliest origins of Leydig progenitors unclear. Additionally, the mechanism by which *NR2F2* is silenced remains unknown, and the effects of NR2F2 loss on androgen output were inferred rather than directly measured. Nonetheless, this study significantly enhances our understanding of testicular development and offers a molecular basis for *NR2F2*-related human DSDs.

DSD Papers: New Insights for the X Chromosome in Men and Women

6.4. How the extra X chromosome impairs the development of male fetal germ cells

Lu Y, Qin M, He Q, Hua L, Qi X, Yang M, Guo Q, Liu X, Zhang Z, Xu F, Ding L, Wu Y, Zhang C, Zhai F, Liu Q, Li J, Yuan P, Shi X, Wang X, Zhao C, Lian Y, Li R, Wei Y, Yan L, Yuan P, Qiao J
Nature. 2024 Nov;635(8040):960-968.
doi: 10.1038/s41586-024-08104-6

Brief summary: This study investigated how the presence of an extra X chromosome in Klinefelter syndrome (47,XXY) affects the development of male fetal germ cells. Using single-cell RNA sequencing and epigenetic profiling of human fetal testes, the authors found that male germ cells with an extra X chromosome exhibit aberrant gene expression, impaired cell cycle regulation, and defective epigenetic reprogramming. They have shown a widespread transcriptional dysregulation in XXY germ cells, including activation of stress and apoptotic pathways. Their findings suggested that human fetal germ cells do not re-establish X-inactivation after X chromosome reactivation (XCR), resulting inpersistent expression from two active X chromosomes. Additionally impaired DNA methylation dynamics and chromatin remodeling compromise germ cell maturation and subsequently many XXY germ cells are eliminated before completing differentiation. Especially, WNT pathway and TGF-β pathway (particularly the NODAL signalling pathway) genes were upregulated which have an important role in maintaining the naive state of fetal germ cells. They have shown that inhibition of the TGF-β pathway improves the differentiation of fetal germ cells in Klinefelter syndrome.

This study provides a detailed molecular map of development of fetal germ cell in Klinefelter syndrome, identifying stage-specific transcriptional defects. It highlights the unique epigenetic behavior of human fetal germ cells, contrasting with mouse models where X-inactivation is more tightly regulated. The rescue experiment with TGF-β inhibition adds translational value and opens the door for interventional strategies in KS-related infertility. However, the long-term functional competence of rescued fetal germ cell (via TGF-β inhibition) was not addressed, and the questions remains whether these cells can give rise to functional spermatogonia or sperm? Additionally, therapeutic translation is promising but issues like safety, timing, and specificity of pathway inhibition need substantial further investigation.

6.5. Aging activates escape of the silent X chromosome in the female mouse hippocampus

Gadek M, Shaw CK, Abdulai-Saiku S, Saloner R, Marino F, Wang D, Bonham LW, Yokoyama JS, Panning B, Benayoun BA, Casaletto KB, Ramani V, Dubal DB
Sci Adv. 2025 Mar 7;11(10):eads8169.
doi: 10.1126/sciadv.ads8169

Brief summary: This study explored emerging evidence suggesting that the inactive (or 'silent') X chromosome in females may contribute to greater brain resilience compared to males.

The authors used a genetic mouse model to investigate transcriptional activity from the inactive X chromosome (Xi) during aging. By crossing *Mus musculus* and *Mus castaneus* strains, distinguished by frequent SNPs, they enabled allele-specific RNA sequencing (RNA-seq). A targeted deletion of the *Xist* gene on the *M. musculus* X ensured that the *M. castaneus* X was consistently inactivated. This setup allowed precise identification of "escapee" genes, those transcribed from the typically silent Xi.

Using single-nucleus RNA-seq, the researchers analyzed over 40,000 hippocampal nuclei from young and aged female mice. Aging altered gene expression of 926 differentially expressed genes (DEGs), including 29 on the X chromosome. When normalized by gene count per chromosome, the X chromosome showed a disproportionately high number of DEGs, especially in dentate gyrus neurons and oligodendrocytes. Gene ontology analysis revealed that X-linked DEGs were enriched in synaptic and neuronal functions, suggesting a specific role for X-linked gene regulation in cognitive aging.

Among the genes upregulated with age on the active X chromosome (Xa) were *Dmd*, *Cnksr2*, and *Pak3,* genes associated with synaptic structure and human intellectual disability. On the Xi, age-related increases in expression were seen in *Ftx* (a long noncoding RNA involved in XCI and neuroprotection), and in myelination-associated genes such as *Plp1* and *Gpm6b*.

To explore functional consequences, the authors overexpressed *Plp1* in the oligodendrocytes of aged mice using adeno-associated virus (AAV). This targeted intervention improved spatial memory in both sexes without altering general activity or anxiety-like behavior, supporting the idea that Xi-derived *Plp1* expression can have beneficial cognitive effects.

Despite these findings, the authors caution that single-nucleus RNA-seq has limited sensitivity for low-abundance transcripts like those from the Xi. Thus, complementary computational tools were needed to fully capture Xi activity in aging hippocampal cells.

In summary, the study challenges the view of Xi as transcriptionally silent and suggests that partial reactivation of Xi-linked genes in aging may offer compensatory benefits. This mosaic expression could provide females with a unique resilience to cognitive decline, highlighting the influence of sex chromosomes in brain aging and disease resistance.

DSDPapers: A Novel Insight in Epigenetic Regulation of Testicular Development: An Old Disease and a New Association

6.6. Maternal iron deficiency causes male-to-female sex reversal in mouse embryos

Okashita N, Maeda R, Kuroki S, Sasaki K, Uno Y, Koopman P, Tachibana M
Nature. 2025;643, 262–270
doi: 10.1038/s41586-025-09063-2

Brief summary: This study explored the critical link between iron metabolism and male sex determination in mice, focusing on how iron-dependent epigenetic regulation activates the *Sry* gene, a key determinant of testis development.

In mice, *Sry* is expressed in NR5A1^{+} pre-Sertoli cells between embryonic days (E) 10.5 and 12.5, where the histone demethylase KDM3A removes repressive H3K9me2 marks to activate its transcription. Since KDM3A requires Fe^{2+} to function, the authors investigated whether iron metabolism influences this process. Using mouse and human single-cell RNA sequencing, they found that genes involved in iron uptake (e.g., *Tfrc*, *Scara5*) and Fe^{2+} production (e.g., *Steap3*, *Ncoa4*, *Hmox1*) are highly enriched in NR5A1^{+} pre-Sertoli cells. Protein and imaging analyses confirmed that these cells accumulate labile iron at E11.5, and iron quantification showed significantly higher iron content in gonadal somatic cells than in surrounding tissues.

To test functional relevance, the authors deleted *Tfrc* (encoding the iron transporter TFR1) in gonadal somatic cells. Loss of TFR1 reduced Fe^{2+} levels, elevated H3K9me2 marks at the *Sry* promoter, and halved *Sry* expression. Despite normal somatic cell numbers, chromatin immunoprecipitation revealed failed H3K9me2 demethylation, linking TFR1-mediated iron uptake to KDM3A activity and *Sry* activation. Functionally, this impaired male development; many XY embryos lacking *Tfrc* developed ovaries or ovotestes, mimicking *Kdm3a*-knockout phenotypes. *Ex vivo* gonad culture experiments confirmed that iron depletion using deferoxamine (DFO) reduced *Sry* expression and promoted ovarian characteristics in XY gonads. This effect was reversed by iron supplementation or enforced *Sry* expression. DFO-treated gonads showed increased H3K9me2 levels at the *Sry* locus, supporting the need for iron in KDM3A-mediated epigenetic activation. *In vivo*, maternal iron deficiency, induced via deferasirox (DFX) or a low-iron diet, decreased *Sry* expression and male-to-female sex reversal, especially in genetically sensitized embryos (e.g., *Kdm3a* heterozygotes).

Although *Kdm3a* expression appeared upregulated under iron-deficient conditions, the mechanism remains unresolved. While the results are based on mouse models, they suggest iron is essential for proper epigenetic control during testis determination. This study introduces maternal iron status as a potentially modifiable environmental factor contributing to DSDs, emphasizing the broader developmental importance of micronutrient availability during pregnancy.

DSD Papers: Testicular-OvotesticularDSD

6.7. Phenotypes linked to duplication upstream of SOX9: new insights into presentation and diagnosis

Unal E, Tekmenuray-Unal A, Cayir A, Papatya Cakir ED, Beyazit N, Kolbasi B, Gurpinar Tosun B, Yigit G, Zibat A, Wollnik B, Demirbilek H, Guran T

J Clin Endocrinol Metab. 2025 Jan 15:dgaf020.
doi: 10.1210/clinem/dgaf020

Brief summary: This study describes twelve 46,XX individuals carrying heterozygous duplications upstream of *SOX9*, ranging from 107–941kb, identified via karyotyping, targeted genetic panels, microarrays, multiplex ligation-dependent probe amplification (MLPA), or whole-genome sequencing. Among them, 7 (58%) exhibited testicular or ovotesticular DSD, while 5 (42%) were asymptomatic carriers, discovered during family screening. There was no clear correlation between duplication size and clinical phenotype. Familial inheritance was found, 3 from fathers and 2 from asymptomatic mothers, and in one case, the duplication had been missed by a 300K microarray but detected by MLPA and a 750K microarray.

The study highlights that the phenotype of 46,XX individuals with upstream *SOX9* duplications can range from complete gonadal sex reversal to asymptomatic carrier. From a genetic counseling standpoint, identifying asymptomatic 46,XX and 46,XY individuals carrying duplications upstream of *SOX9* is just as crucial as accurately diagnosing the index case. This recognition enables informed reproductive decisions and supports the use of preimplantation genetic diagnosis to promote healthy future generations. Additionally, high-resolution microarrays (>500K) are recommended as the diagnostic method of choice for 46,XX SRY-negative individuals suspected of DSD, as they can detect both large and small copy-number variants effectively.

The presence of asymptomatic carriers suggests variable penetrance, but the study did not explore molecular or environmental modifiers that might explain why some carriers are unaffected. Therefore, mechanisms underlying this phenotypic variability remain unclear. In conclusion, this study expands the clinical and diagnostic spectrum of *SOX9* upstream duplications in 46,XX DSD but is limited by small sample size and lack of mechanistic insight.

6.8. Is it possible to separate the testicular and ovarian components of an ovotestis?

Baskin L, Cao M, Li Y, Baker L, Cooper C, Cunha G
J Pediatr Urol. 2025 Apr 17:S1477-5131(25)00181-0.
doi: 10.1016/j.jpurol.2025.04.009

Brief summary: This clinical study investigated whether it is surgically feasible to separate the testicular and ovarian components within an ovotestis. Ovotestes, found in individuals with ovotesticular DSD, contain both seminiferous tubules and ovarian follicles and exist in mixed or bipolar configurations. The authors examined 20 human gonadal specimens originally diagnosed as ovotestes. Upon re-sectioning and retesting with markers for testicular tissue (SOX9, TSPY, etc.) and ovarian tissue (FOXL2, DDX4), six specimens did not have ovarian presence. Of the remaining 14 specimens from 13 patients, 7 provided full gonadal cross-sections suitable for analysis of potential separation planes. Histology revealed a complex intermingling of testicular and ovarian structures, with follicles often encircling seminiferous cords and mixed tissue layers in between, indicating no clear boundary for surgical dissection.

In partial biopsy specimens, a similar absence of a distinct separation plane was found. The ovarian and testicular tissues were intimately interwoven, preventing "'clean' surgical excision" of either component without removing adjacent tissue of the other type. Based on this anatomical analysis, the authors concluded that it is *not feasible* to surgically isolate testicular or ovarian tissue from human ovotestes without leaving behind tissue discordant with the patient's gender identity.

Limitations of the study include the limited sample size, which may not cover the full range of anatomical variation, especially in the rarer bipolar ovotestes, leaving open the possibility that some rare anatomical configurations may allow for separation. Secondly, the study is based solely on retrospective histological evaluation rather than clinical surgical outcomes. While informative, histology alone cannot confirm whether alternative approaches (e.g., dissection guided by intraoperative imaging or microsurgical techniques) might allow cleaner separation with acceptable functional outcomes. Lastly, the investigation did not assess actual surgical or reproductive consequences of preserving mixed gonadal tissue. As a result, the impacts on hormonal function, fertility, risk of gonadectomy, patient gender identity satisfaction, or tumorigenic potential of residual tissue remain unanswered. Multidisciplinary

studies combining histology with *in vivo* imaging, intraoperative assessment, and long-term follow-up are needed to fully evaluate the potential, and risks, of conservative approaches in managing ovotestis.

DSD Papers: DSD associated with Rare Mitochondrial Disorders

6.9. LARS2-Related perrault syndrome in siblings with 46,XY differences of sex development

Adam AP, O'Sullivan L, Peterson A, Yabumoto M, Merguerian P, Adam MP
Am J Med Genet A. 2025 Mar 22:e64064.
doi: 10.1002/ajmg.a.64064

Brief summary: This case report describes 2 brothers with a 46,XY karyotype who exhibit *LARS2*-related Perrault syndrome, a condition traditionally defined by sensorineural hearing loss and ovarian dysgenesis in 46,XX individuals. The brothers presented with bilateral hearing loss, bilaterally undescended testes, and hypospadias with chordee in the younger brother. Trio exome sequencing identified biallelic pathogenic variants in *LARS2*, a mitochondrial leucyl-tRNA synthetase gene previously linked to Perrault syndrome. No other genetic variants were found, strongly implicating *LARS2* mutations as the cause of both their hearing loss and undervirilized genital phenotype, which extends the phenotypic spectrum of Perrault syndrome to include 46,XY DSD.

The findings suggest that *LARS2*, being expressed in gonadal tissue, plays a role in testis development or function. Although the full mechanisms remain undefined, defects in mitochondrial translation due to LARS2 dysfunction may impair testicular differentiation, resulting in undervirilization. The authors recommend including *LARS2* in the gene panel for DSDs, particularly for 46,XY individuals with hearing loss and mild external genital anomalies.

6.10. Primary adrenal insufficiency in patients with *CPOX* gene mutations

Kelestemur E, Yarar MH, Gurpinar Tosun B, Karaca M, Goler AMY, Yilmaz BK, Yapici O, Gokcay G, Guran T
Eur J Endocrinol. 2025 Apr 30;192(5):K31-K37.
doi: 10.1093/ejendo/lvaf089

Brief summary: This case report describes2 siblings, one 46,XY and one 46,XX, with primary adrenal insufficiency (PAI) in the context of harderoporphyria, a porphyrin metabolism disorder caused by biallelic mutations in the *CPOX* gene. Both children presented early in life with microcytic anemia, cholestasis, hepatosplenomegaly, and neurological symptoms such as nystagmus and optic atrophy. They were later diagnosed with PAI at ages 4.5 years and 7 months. The patient with 46,XY karyotype also had DSD.

Whole-genome sequencing identified a homozygous frameshift variant (c.83_85del, p.S28^{+}) in the *CPOX* gene, affecting coproporphyrinogen oxidase. Biochemical assays showed dysfunctional mitochondrial membrane potential in patient cells, suggesting that CPOX deficiency impairs mitochondrial steroidogenesis, leading to deficiencies in CYP11A1 and CYP11B1 activity and resulting in PAI and 46,XY DSD. The diagnosis of combined CYP11A1 and CYP11B1 deficiency remains inferred from hormonal profiles, without direct demonstration of impaired enzyme activity or reduced steroidogenic output in adrenal cells. Additionally, while mitochondrial dysfunction was observed in peripheral blood cells, there was no direct assessment of adrenal tissue, which limits interpretation of how *CPOX* mutation specifically disrupts steroidogenesis. A similar phenotype has been described by Honda M, *et al*. in 2 new patients with PAI and 46,XY DSD due to biallelic rare *CPOX* variants (1).

In summary, this report expands the phenotypic spectrum of CPOX-related harderoporphyria to include PAI and DSD, likely via impaired mitochondrial steroidogenesis and affecting adrenal and gonadal function. However, broader studies with functional adrenal assays and larger cohorts are needed to confirm causality and elucidate pathophysiological mechanisms. Any form of inherited mitochondrial dysfunction, whether caused by defects in mitochondrial DNA or autosomal genes encoding mitochondrial proteins, can cause impaired adrenal and

gonadal steroidogenesis which can lead to adrenal insufficiency and DSD. It is important to recognize that the symptoms of the primary disease may overlap with or mask those of adrenal insufficiency. This is particularly critical in preventing mortality associated with unrecognized adrenal failure.

Reference

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6.11. *FDXR* variants cause adrenal insufficiency and atypical sexual development

Pignatti E, Slone J, Gómez Cano MÁ, Campbell TM, Vu J, Sauter KS, Pandey AV, Martínez-Azorín F, Alonso-Riaño M, Neilson DE, Longo N, du Toit T, Voegel CD, Huang T, Flück CE

JCI Insight. 2024 Jun 17;9(14):e179071.

doi: 10.1172/jci.insight.179071

Brief summary: This study identified biallelic variants in the ferredoxin reductase gene (*FDXR*), encoding mitochondrial flavoprotein, as a newly recognized cause of adrenal insufficiency and atypical sex development. Previously, *FDXR* mutations were linked to neurodegenerative disorders (ferredoxin reductase-related mitochondriopathy, FRM), but adrenal dysfunction was not documented. In two 46,XX siblings with FRM, homozygous p.G437R *FDXR* mutations led to ambiguous genitalia, cortisol deficiency, and androgen excess reminiscent of 11β-hydroxylase deficiency. Both infants died within their first year of life, likely due to adrenal crises triggered by infections.

Functional studies in patient-derived adrenal-like cells showed impaired glucocorticoid and mineralocorticoid synthesis, confirming FDXR's role in steroidogenesis via its support of mitochondrial CYP enzymes such as CYP11A1, CYP11B1, and CYP11B2. Additionally, a mouse model carrying an orthologous *Fdxr* mutation (p.R389W) exhibited reduced corticosterone and progesterone levels, yet maintained normal adrenal zonation, indicating preserved structural integrity despite functional impairment.

Collectively, these findings expand FRM's clinical spectrum to include a form of syndromic 46,XX adrenal insufficiency with steroidogenic defects. They highlight the importance of evaluating both sexes in mitochondrial-linked endocrine disorders and suggest that acute or subclinical adrenal insufficiency in FRM could be life-threatening under stress.

With the increasing use of advanced molecular diagnostic techniques, both the number of reported cases with mitochondriopathies, and the list of associated genes continue to expand (1).

Reference

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DSD Papers: Long-Term Outcomes of Feminizing Genitoplasty in DSD

6.12. Long-term outcomes of feminizing genitoplasty in DSD: genital morphology, sensitivity, sexual function, and satisfaction

Bag MJ, Inacio M, Bachega TASS, Batista RL, Madureira G, Costa EMF, Domenice S, Mendonca BB, Dénes FT, Sircili MHP

J Endocr Soc. 2025 Feb 19;9(3):bvaf014.

doi: 10.1210/jendso/bvaf014

Brief summary: This retrospective cohort study evaluated long-term outcomes in 60 DSD patients who underwent feminizing genitoplasty in Brazil between 1965 and 2016. The cohort included 36 with CAH and 24 with non-CAH etiologies. The median follow-up age was 25 years, with a median follow-up duration of 12 years.

This study assessed genital morphology, sensation, sexual function, and satisfaction of the participants. Most patients had a visible clitoris (91%) and 2 separate perineal openings (85%), with 80% requiring no further surgery. Surgical complications, including persistent urogenital sinus, vaginal stenosis, and clitoromegaly, were relatively uncommon, and reoperation was needed in 18%. Advances in surgical technique, such as dorsal neurovascular bundle (DNVB) preservation and refined urogenital sinus repair, contributed to improved outcomes.

Sensory testing showed that genital sensitivity was largely preserved. While non-CAH patients had slightly lower clitoral touch sensitivity, this did not impact overall function. Sexual function scores were within the normal range, and successful intercourse and pregnancies were reported among CAH patients. High satisfaction rates were observed among both patients and parents, with many favouring early surgery. Notably, better vaginal, rather than clitoral, sensitivitycorrelated more strongly with sexual satisfaction, highlighting its importance in this cohort. While limitations include the retrospective nature of surgical data and variability in techniques over time, this study's long follow-up and consistent evaluations strengthen its conclusions.

The study emphasizes the value of individualized, multidisciplinary care integrating surgery, endocrinology, and psychological support. Despite overall positive outcomes, the optimal timing of surgery remains debated. The dsd-LIFE study, a large multicenter analysis of 174 women with classical CAH, reported dissatisfaction and complications in a subset of cases who undergone early FGS. It stressed the importance of fully informing families about potential risks and supporting the option to delay surgery (2).

In summary, FGS can offer favourable long-term results in selected cases when performed by experienced teams using modern techniques, but careful case-by-case decision-making and family counselling remain essential.

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DSD Papers: Phenotypic Variation and Pubertal Outcomes In 46,XY Gonadal Dysgenesis

6.13. Phenotypic variation and pubertal outcomes in males and females with 46,XY partial gonadal dysgenesis

Tadokoro-Cuccaro R, Hughes IA, Cools M, van de Vijver K, Bilharinho de Mendonça B, Domenice S, Loch Batista R, Thomazini Dallago R, F Costa E, Lisboa Gomes N, T Maciel-Guerra A, Guerra-Junior G, Gabriel Ribeiro de Andrade J, Lucas-Herald A, Bryce J, Hannema S, Juul A, Globa E, McElreavey K, Baronio F, Rey R, Lopez Dacal J, Darendeliler F, Poyrazoglu S, Kolesińska Z, Niedziela M, Claahsen-van der Grinten HL, L T van den Akker E, Herrmann G, Atapattu N, Jain V, 1Sharma R, Bettendorf M, Konrad D, Lenherr-Taube N, Holterhus PM, Fica S, Skae M, Russo G, Stancampiano MR, Gazdagh G, Davies JH, Mohamed Z, Seneviratne SN, Güran T, Güven A, Wasniewska M, Mladenov V, Verkauskas G, Markosyan R, Korbonits M, Hiort O, Frielitz-Wagner IV, Ahmed SF, Thankamony A

J Clin Endocrinol Metab. 2025 Apr 10:dgaf223.
doi: 10.1210/clinem/dgaf223

Brief summary: This international, multicenter study analyzed 310 individuals with 46,XY gonadal dysgenesis (GD), subdivided into complete (CGD) and partial forms (PGDf assigned female and PGDm assigned male). CGD patients typically presented with delayed puberty and elevated gonadotropins, while PGD cases were often diagnosed in infancy due to atypical genitalia. PGDm had more masculinized genitalia compared to PGDf. Müllerian structures were common in CGD and less frequent in PGD, reflecting differences in gonadal development. Comorbidities, particularly renal and neurodevelopmental, were prevalent, especially among those with *WT1* mutations. Hormonal profiles confirmed impaired gonadal function, with CGD individuals showing the lowest testosterone, AMH, and inhibin B levels.

Genetic analysis identified causative mutations in 42.3% of participants, with *SRY* and *WT1* variants predominant in CGD, while *NR5A1* mutations were common in PGD, especially PGDm, and linked to spontaneous puberty. Pubertal outcomes varied: 80% of PGDm entered puberty naturally, with 59% reaching Tanner stage G5 without hormone therapy. In contrast, most with CGD required estrogen therapy. PGDf cases often showed both breast development and virilization.

Surgical interventions were frequent: PGDf typically underwent clitoral reduction and vaginoplasty; PGDm had orchidopexy and hypospadias repair. Gonadectomy was common, especially in CGD where tumor risk, highest with intra-abdominal gonads, was a major concern. Histology confirmed streak or dysgenetic gonads in many.

Sex reassignment occurred in 16.1% of PGDf and 5.3% of PGDm, mostly from female to male, with timing varying by region and cultural factors. The wide phenotypic spectrum of PGD, from female to near-male, complicates classification and management.

Despite advances in genetic testing, many cases remain unexplained. Individualized care, informed by phenotype, gonadal function, and local context, remains essential. This study highlights the need for multidisciplinary teams, careful tumor risk assessment, and long-term follow-up in managing 46,XY gonadal dysgenesis.

Gender Incongruence: Immune System Adaptation during Gender-Affirming Testosterone Treatment

6.14. Immune system adaptation during gender-affirming testosterone treatment

Lakshmikanth T, Consiglio C, Sardh F, Forlin R, Wang J, Tan Z, Barcenilla H, Rodriguez L, Sugrue J, Noori P, Ivanchenko M, Piñero Páez L, Gonzalez L, Habimana Mugabo C, Johnsson A, Ryberg H, Hallgren Å, Pou C, Chen Y, Mikeš J, James A, Dahlqvist P, Wahlberg J, Hagelin A, Holmberg M, Degerblad M, Isaksson M, Duffy D, Kämpe O, Landegren N, Brodin P
Nature. 2024 Sep;633(8028):155-164.
doi: 10.1038/s41586-024-07789-z

Erratum in: Nature. 2024 Oct;634(8033):E5.
doi: 10.1038/s41586-024-08081-w

Brief summary: This study examined changes in the immune system in 23 adult transgender men (female sex registered at birth) during the first year of testosterone treatment. Bulk mRNA sequencing of whole blood showed downregulation of hallmark interferon alpha responses and upregulation of tumour necrosis factor signalling through NFkappaB and Hallmark inflammatory responses. These changes were related to changes in the number and function of plasmacytoid dendritic cells, monocytes and natural killer cells. Analysis of existing datasets on immune responses in cisgender males and females supported the role of sex hormones in regulation of the IFN-I/TNF axis.

The study helps to tease apart the contribution of hormonal as opposed to genetic and behavioural factors to sex differences in the immune system, and in infectious, inflammatory and auto-immune conditions. The finding that testosterone alters the IFN-1/TNF axis, as previously reported (1), with an increased pro-inflammatory response, may explain the higher risk of cytokine storm and increased mortality from severe infections among men from the general population.

For transgender men, the results suggest that testosterone treatment may increase the risk of severe infections. One Turkish questionnaire-based study among 179 transgender men and 59 transgender women found that transgender men on testosterone were 3.46 times more likely than transgender women on estrogen to have contracted COVID-19 vs a 1.01 ratio of women to men in the general Turkish population (2). However, most reported a mild course of the disease with none admitted to the intensive care. A previous study from the Netherlands reported no deaths from infectious diseases among 1641 transgender men who had started testosterone treatment at a median age of 23 years (IQR 20-32), but given the follow-up time of median 5 years (IQR 2-17) this was still a relatively young population (3).

Another recent study reported that testosterone affected CD4+ T-cell function in transgender men which might be relevant for the risk of auto-immune conditions (4) and a registry-based study reported prescription of gender affirming hormone treatment was associated with an increased incidence rate of auto-immune disease in transgender men (5). Future studies will have to confirm if and how testosterone treatment alters morbidity and mortality from infections and auto-immune diseases in transgender men.

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6.15. Estrogen influences class-switched memory B cell frequency only in humans with two X chromosomes

Peckham H, Radziszewska A, Sikora J, de Gruijter NM, Restuadi R, Kartawinata M, Martin-Gutierrez L, Robinson GA, Deakin CT, Wedderburn LR, Jury EC, Butler G, Chambers ES, Rosser EC, Ciurtin C

J Exp Med. 2025 Apr7;222(4):e20241253.

doi: 10.1084/jem.20241253

Brief summary: This study identified that among immune cell types in peripheral blood, sex differences were largest for CD19+CD27+IgD- class-switched memory B-cells, with higher numbers in females. This difference aroseonly after puberty and was no longer present after menopause. Transgender males on GnRH analogue treatment had lower numbers of these cells than control females, and postmenopausal women on estrogen treatment had higher numbers compared to untreated controls, further supporting an important role of estrogens in the regulation of this cell type. However, this only seemed to apply to XX females, as 20 transgender female adolescents (male sex registered at birth) treated with a GnRH analogue and estradiol had similar numbers of CD19+CD27+IgD- class-switched memory B-cells to control males.

Females have a higher risk of autoimmunity and for several autoimmune conditions this risk increases from pubertal age. The results of this study suggest that the influence of estrogen on CD19+CD27+IgD- class-switched memory B-cells may be an underlying mechanism. Estradiol treatment (mean duration 13 months, range 4.5-23) did not affect the number of these cells in transgender female adolescents, which the authors attributed to their XY chromosome complement. However, the dose or serum concentrations of estradiol were not reported. As previous studies have shown low serum estradiol concentrations in transgender adolescents treated with a standard pubertal induction protocol (1) it would be interesting to investigate if estradiol dose may also play a role.

Clinical studies have also investigated the risk of autoimmunity in transgender people. A recent register-based Danish study reported that before diagnosis, transgender females had an incidence rate ratio (IRR) of 1.35 (95%CI 1.04-1.77) for any autoimmune disease and 1.66 (95%CI 1.05-2.61) for type 1 diabetes mellitus compared to male controls, which the authors suggested may be related to minority stress. After diagnosis, the IRR for thyroid disease was 1.98 (95%CI 1.09-3.61) but no association was found between prescription of gender affirming hormones and the incidence of autoimmune disease in transgender females.

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Gender Incongruence: Sex Hormones and Kidney Function

6.16. Unveiling mechanisms underlying kidney function changes during sex hormone therapy

van Eeghen SA, Pyle L, Narongkiatikhun P, Choi YJ, Obeid W, Parikh CR, Vosters TG, van Valkengoed IG, Krebber MM, Touw DJ, den Heijer M, Bjornstad P, van Raalte DH, Nokoff NJ

J Clin Invest. 2025 Mar 25;135(9):e190850.

doi: 10.1172/JCI190850

Brief summary: This prospective study assessed changes in kidney function in 23 transgender women (registered sex at birth male) and 21 transgender men. In transgender women GFR (measured using iohexol clearance) increased by 3.6% and effective renal plasma flow (ERPF, measured via para-aminohippuric acid clearance) increased by 9.1% during three months of feminising hormone treatment (estradiol and an anti-androgen). Several tubular injury biomarkers decreased. In transgender men no significant changes of GFR or ERPF were observed during three months of testosterone treatment whereas two tubular injury biomarkers increased. Proteomic analysis identified potential mediators of the effects of sex steroids.

Previous studies have reported changes in kidney function parameters such as creatinine and cystatin C in transgender individuals undergoing hormone treatment, but these are also influenced by body composition. In addition, when estimating GFR from creatinine or cystatin C, different formulas are used for male or female sex, which produce substantially different results (1). This complicates their use in the assessment of kidney function in transgender people. The recent study by van Eeghen *et al*. used the gold-standard methods to measure GFR and ERPF. The observed enhanced kidney function during feminising hormone treatment did not seem to be associated with glomerular hyperfiltration but rather suggested a state of afferent vasodilation induced by increased estradiol and decreased testosterone concentrations. A renoprotective effect of estradiol may explain the slower progression of chronic kidney disease in women compared to men. What the clinical significance is of the increased level of two kidney injury biomarkers that may indicate tubular stress in transgender men deserves further study.

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Gender Incongruence: Sexual Functioning in Transgender Adults who received GnRH Analogue Treatment In Adolescence

6.17. Timing of puberty suppression in transgender adolescents and sexual functioning after vaginoplasty

van der Meulen IS, Bungener SL, van der Miesen AIR, Hannema SE, Kreukels BPC, Steensma TD, Bouman MB, de Vries ALC

J Sex Med. 2025 Jan 3;22(1):196-204.

doi: 10.1093/jsxmed/qdae152

Brief summary: This retrospective questionnaire-based study explored sexual functioning and difficulties among 37 transgender women (male sex registered at birth) who had started treatment with a GnRH analogue in

adolescence followed by estogen treatment and vaginoplasty. The large majority experienced sexual desire (91%), arousal (86%) and orgasm (78%). Although those treated from early puberty (Tanner stage G2-3, n = 16) had less commonly experienced orgasm before surgery compared to those who had started treatment in late puberty (Tanner stage G4-5, $n = 21$) (19 vs 58%), the percentage was comparable after surgery (87 vs 71%).

This study addresses a knowledge gap (1), on outcomes with regard to sexual function and dysfunction after GnRH analogue treatment in adolescence for gender dysphoria. Outcomes were similar to those previously described for transgender individuals who started medical treatment in adulthood. While the sample size was small and findings need to be confirmed in larger studies, the results suggest that GnRH analogue treatment to suppress puberty may not have a lasting impact on the ability to experience sexual desire, arousal and orgasm. At the same time, sexual difficulties were common among those that had sexual intercourse ($n = 21$), with 52% experiencing pain during intercourse. A second study by van der Meulen *et al*. (2) that also included transgender men that had received GnRH analogue treatment in adolescence ($n = 50$), found that sexual dysfunction was common among transgender men too (58%), with difficulty initiating sexual contact being the most frequently reported. No difference was observed between those who had started treatment in early (Tanner stage B2-3) vs late (Tanner stage B4-5) puberty (67 vs 56%), although again groups were small. Sexual satisfaction was found to be comparable to that in the general population.

These first studies on sexual outcomes will be informative when counselling transgender adolescents and their parents considering hormonal treatment. They also point out the need to provide ongoing support to address sexual difficulties that transgender individuals encounter, which are not only related to physical complaints but also frequently to psychosocial challenges.

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Gender Incongruence: Transgender Care - Opportunities and Threats

6.18. Endocrine management of transgender and gender-diverse adolescents: expert opinion of the espe working group on gender incongruence and the Endo-ERN main thematic group on sexual development and maturation

Hannema SE, Busiah K, Butler G, Claahsen-van de Grinten HL, Cools M, Gawlik-Starzyk AM, Klink D, Main KM, Martinerie L, Richter-Unruh A, Skordis N, de Vries MC

Horm Res Paediatr. 2024 Dec 2:1-27.
doi: 10.1159/000542904

Brief summary: This publication, the result of a collaboration between ESPE and Endo-ERN, summarises recent evidence on hormonal treatment of transgender and gender-diverse adolescents and provides practical information and tools for paediatric endocrinologists providing this care. Topics include the importance of multidisciplinary care, counselling prior to treatment, fertility preservation, options for hormonal treatment, long-term follow-up and transition of care, altered treatment wishes, lifestyle counselling, sexual health and contraception and ethical considerations.

In addition to this document, the last year has seen the publication of a number of national guidelines and expert consensus papers on endocrine treatment of transgender adolescents, for example from France (1), Germany (2) and Poland (3), aiming to improve care. At the same time, gender affirming care has been restricted or banned in other countries such as the United States (4). Several National Institute of Health grants for research on transgender health among other topics were cancelled (5), although a judge recently ruled that the terminations had no legally valid basis (6). A presidential action stated that “Female” means a person belonging, at conception, to the sex that produces the large reproductive cell and “Male” means a person belonging, at

conception, to the sex that produces the small reproductive cell' (7). This action, aimed against 'gender ideology extremism' does no right to either transgender people or individuals with differences of sex development. Therefore, now more than ever, health care professionals and scientists need to make clear that reality is more complex and nuanced than this and continue to strive for evidence-based care that is accessible to all that need it.

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7. Puberty

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Introduction

This year's publications highlight puberty's intricate regulation by genetic, metabolic, and environmental factors. Urinary estrone emerges as a potential biomarker of metabolic risk in adolescent girls, while DLK1 dynamics and urinary LH offer insights into pubertal staging. The COVID-19 pandemic revealed a surge in central precocious puberty (CPP), prompting investigation into psychosocial and behavioral triggers. Genetic studies identified novel candidates for delayed puberty. Neuroendocrine research uncovered how hypothalamic lipid-sensing and AgRP–Kisspeptin circuits mediate nutritional influences on pubertal timing. Finally, Mendelian randomization linked early puberty to adverse adult metabolic profiles, and rare variants in DNA repair genes connected reproductive ageing to cancer risk and intergenerational effects. Together, these findings redefine puberty as a critical window for lifelong health programming.

Clinical Guidance and Studies

7.1. Urinary estrogens in girls throughout puberty as a marker of metabolic risk and their relationship with premature adrenarche

Zepeda D, Pereira A, Iniguez G, Mericq V
Clin Endocrinol (Oxf). 2025 Jun;102(6):656-663.
doi: 10.1111/cen.15215. PMID: 39930933.

Brief summary: This prospective study reports a positive correlation between urinary estrone levels during late puberty and both adiposity and metabolic risk in 321 Chilean girls. This association was absent in girls with premature adrenarche, suggesting the involvement of alternative pathways in their metabolic risk.

Premature adrenarche has been linked to increased metabolic risk throughout puberty (1, 2). However, it remains unclear whether these effects are driven by androgens, estrogens, or a combination of both. This study evaluated the association between urinary estrogen levels (estradiol and estrone) and metabolic risk during late puberty, and determined whether this relationship differs between girls with and without premature adrenarche.

Multilevel analysis revealed a positive correlation between urinary estrone levels and body mass index, waist circumference, and body fat percentage at Tanner stage 4, one year post-menarche, and 4 years post-menarche. In contrast, urinary estradiol levels showed no such association. Similarly, estrone concentrations were positively correlated with the metabolic syndrome score (MetS score), whereas estradiol concentrations were not. In girls with premature adrenarche (defined by elevated DHEA-S levels at age 7), neither estrone nor estradiol levels were correlated with the MetS score.

These findings suggest that, in adolescent girls, metabolic risk may be mediated in part by estrogens, particularly estrone, highlighting its potential role as a biomarker of metabolic risk. Moreover, the lack of association

between urinary estrogens and MetS score in girls with premature adrenarche suggests the potential role of androgens in their metabolic disturbances.

Taken together, these results support the existence of distinct biological pathways underlying metabolic risk during puberty in girls with and without premature adrenarche.

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7.2. Serum DLK1 during minipuberty and pubertal transition in healthy girls and in girls with precocious puberty

Vilmann L, Sørensen K, Busch AS, Ljubicic ML, Upners EN, Fischer MB, Johannsen TH, Holmboe SA, Juul A, Hagen CP

J Clin Endocrinol Metab. 2025 May 19;110(6):1570-1576.

doi: 10.1210/clinem/dgae762. PMID: 39468766.

Brief summary: This longitudinal study evaluated changes in DLK1 serum levels in healthy girls during infancy and puberty. DLK1 was also measured in girls with central precocious puberty (CPP) before and after treatment with GnRH agonists (GnRHa)

DLK1 plays a critical inhibitory role in the Delta Notch pathway regulating reproductive and metabolic systems (1). Pathogenic variants in *DLK1* have been found in children presenting CPP (2) but data regarding serum DLK1 levels changes during pubertal development in healthy girls or girls with CPP is scarce.

Median DLK1 levels were measured sequentially in healthy infant girls ($n=85$), in healthy peripubertal girls ($n=15$) and in girls with CPP before and after GnRHa treatment ($n=15$) from 3 Danish longitudinal cohorts. Median serum concentrations of DLK1 levels declined markedly through the first year of life (from 17.6 ng/ml to 9.9 ng/ml, $P=0.02$). Serum DLK1 levels were similar in girls in late infancy and before pubertal onset (10 ng/ml and 10.7 ng/ml, $P=0.093$). In girls with normal pubertal development, serum DLK1 levels decreased as puberty progressed. In girls with CPP, circulating DLK1 levels remained unchanged during treatment with GnRH. In the first available individual sample in infant girls (median age 44 days) and in healthy peripubertal girls (median age 9.4 years), DLK1 was inversely correlated with birthweight and body fat percentage.

This study demonstrates that DLK1 levels decline during infancy, remain stable in childhood, then decrease again with the onset of puberty, and continue to decrease throughout pubertal development. However, due to the high interindividual variability in DLK1 concentrations at the onset of puberty, it is not possible to establish a reliable cutoff level to distinguish between prepubertal and pubertal girls. Hence, DLK1 serum level is not a reliable diagnostic marker for puberty onset.

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7.3. Comparison of central precocious puberty frequency before and during COVID-19: a systematic review and meta-analysis

Zhang J, Xu J, Tang X, Wu R

BMC Endocr Disord. 2024 Oct 17;24(1):219.

doi: 10.1186/s12902-024-01749-4. PMID: 40015255

Brief Summary: This systematic review and meta-analysis included 17 retrospective studies assessing central precocious puberty (CPP) incidence before and during the COVID-19 pandemic. The pooled analysis revealed a marked increase in CPP diagnoses during the pandemic (OR = 2.57; 95% CI = 1.85–3.56), with no major difference in clinical features.

During the COVID-19 pandemic, multiple centers reported an increase in CPP diagnoses (1). This meta-analysis combined data from 17 retrospective studies including over 18,000 children from 8 countries, comparing CPP frequency before and during the pandemic. The results confirmed a markedly higher rate of CPP during the pandemic period.

Interestingly, this increase was not accompanied by changes in age at diagnosis, bone age advancement, BMI SDS, or basal LH levels. This suggests that the rise in diagnoses is unlikely to be due to changes in clinical presentation or earlier identification by the parents. The authors discuss various hypotheses, including increased psychosocial distress/isolation (2), or change in habits with a decrease in outdoor activity and increase in exposure to electronic devices.

In conclusion, there was a marked elevation in CPP frequency throughout the COVID-19 pandemic. While causality cannot be established from retrospective data, these findings underscore the importance of investigating modifiable environmental and behavioral factors influencing pubertal timing. It remains to be determined whether those trends have since reversed or are continuing.

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7.4. Comprehensive study on central precocious puberty: molecular and clinical analyses in 90 patients

Hiromune N, Tomoe O, Hideaki Y, Keisuke N, Tatsuki U, Tomohiro S, Shun S, Saori K, Shinichiro S, Mitsukazu M, Shintaro T, Sumito D, Satoshi N, Yasuhiro N, Reiko H, Tsutomu O, Maki F, Masayo K

J Clin Endocrinol Metab. 2025 Mar 17;110(4):1023-1036.

doi: 10.1210/clinem/dgae666. PMID: 39324648

Brief summary: This multicenter cohort study recruited 90 patients with idiopathic central precocious puberty (CPP) and normal brain MRI. Using molecular analyses (targeted sequencing, methylation analysis, and aCGH), the authors identified potential (epi)genetic causes in 12.2% of cases.

CPP can be associated with various pathogenic gene variants, as well as imprinting disorders such as Temple syndrome (TS14) or Silver-Russell syndrome (1). In this Japanese study, 90 patients with CPP (81 sporadic, 9 familial) underwent targeted sequencing of *MKRN3, DLK1, MECP2, KISS1* and *KISS1R*, alongside methylation analysis to screen for associated imprinting disorders. 11 of 90 patients had identifiable (epi)genetic causes: 8 with TS14 (6 epimutations, 1 UPD(14)mat, 1 microdeletion) and 3 with *MKRN3* defects (1 pathogenic variant, one deletion in the 5′-untranslated region, one microdeletion). Six of the 8 patients with TS14 were born small for gestational age (SGA) and presented with features such as short stature and hypotonia. All *MKRN3*-related cases had a paternal history of early puberty and low circulating MKRN3 levels. No pathogenic variants were identified in *KISS1, KISS1R*, or *MECP2*.

In conclusion, (epi)genetic testing for TS14 and *MKRN3* defects should be considered in CPP patients born SGA or paternal familial CPP, respectively. TS14 can be underdiagnosed due to nonspecific clinical features (2), but genetic diagnosis is crucial for appropriate management and long-term follow-up. This study reinforces the importance of imprinted gene regulation in pubertal timing.

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7.5. Deleterious variants in intolerant genes reveal new candidates for self-limited delayed puberty

Rezende RC, He W, Kaisinger LR, Lerario AM, Schafer EC, Kentistou KA, Barroso PS, Andrade NLM, Dantas NCB, Costa EMF, Cellin LP, P S Quedas E, Seminara SB, Rey RA, Grinspon RP, Meriq V, Ong KK, Latronico AC, Perry JRB, Howard SR, Chan YM, Jorge AAL

Eur J Endocrinol. 2025 Mar 27;192(4):481-490.
doi: 10.1093/ejendo/lvaf061. PMID: 40193575.

Brief summary: Using whole-exome sequencing in 71 patients, this study identified 19 novel candidate genes potentially involved in self-limited delayed puberty. Self-limited delayed puberty (SLDP) is the most common cause of pubertal delay and is highly heritable, yet its genetic basis remains poorly understood (1). While genome-wide association studies have identified common variants influencing pubertal timing (2), few rare coding variants have been linked to SLDP. This study aimed to uncover novel candidate genes by performing whole-exome sequencing (WES) in a cohort of children with SLDP, most of whom also presented with short stature.

WES in 71 SLDP patients identified 21 rare high- or moderate-impact variants across 19 candidate genes intolerant to mutation. Eight genes (*GPS1, INHBB, SP3, NAMPT, ARID3B, NASP, FNBP1*, and *PRDM2*) were enriched in SLDP cases compared to gnomAD controls. Notably, *INHBB* was also associated with delayed menarche based on the UK Biobank data. Several variants were found in genes previously linked to growth or pubertal disorders, including *CDK13, GDF5, ANRKD11*, and *GHSR*. Pathway analysis revealed enrichment in TGF-β and GnRH receptor signalling, both central to reproductive maturation.

This study expands the genetic landscape of SLDP, suggesting contributions from oligogenic/polygenic mechanisms. The identification of novel candidate genes, particularly *INHBB*, provides new insights into the biology of pubertal timing and highlights the importance of integrating rare variant analysis with functional and population-level data. These findings may inform future diagnostic and therapeutic strategies for pubertal disorders.

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7.6. Moderate day-to-day variation in first-morning urine total luteinizing hormone levels supports the use of a single determination to identify imminent puberty

Demir A, Hero M, Juul A, Main KM

Clin Endocrinol (Oxf). 2025 May;102(5):578-588.
doi: 10.1111/cen.15208. PMID: 39934096.

Brief summary: This study assessed the clinical reliability of first-morning urinary LH (U-LH) levels to determine pubertal onset. Despite moderate day-to-day variation, a single U-LH measurement was sufficient to classify children as prepubertal, peripubertal, or pubertal.

First-morning urinary gonadotropin measurement offers a non-invasive alternative to serum sampling and GnRH stimulation test for assessing pubertal status. In this semi-longitudinal study of 354 healthy children, U-LH levels were classified as prepubertal ($<$ 0.60 IU/l), highly likely pubertal (0.60–0.99 IU/l), and pubertal ($\geq$ 1.00 IU/l). Demir *et al*. demonstrated that a single U-LH measurement, despite moderate day-to-day variation (~33% coefficient of variation), was sufficient to determine pubertal stage in over 95% of cases, with only 3.6% of boys and 4.9% of girls showing inconsistent classification across three consecutive mornings.

The first increase in mean U-LH concentrations occurred shortly after the age of 10 in both sexes, suggesting that U-LH captures early hypothalamic-pituitary-gonadal axis activation before obvious clinical progression. The findings reinforce earlier data showing that the rise in central gonadotropin secretion often precedes visible pubertal signs, and that the timing of central puberty onset is sex-independent (1).

The findings described in this article are aligned with a study demonstrating that both basal serum LH and single random urinary gonadotropin measurements can aid in the diagnosis of central precocious puberty (2). Although assay standardization and sample handling practices still require refinement, U-LH testing is emerging as a practical, low-burden diagnostic tool. It may serve as a first-line screening method, particularly in outpatient settings where stimulation testing is not feasible.

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7.7. Phenotypic variation and pubertal outcomes in males and females with 46,XY partial gonadal dysgenesis

Tadokoro-Cuccaro R, Hughes IA, Cools M, van de Vijver K, Bilharinho de Mendonça B, Domenice S, Loch Batista R, et al
J Clin Endocrinol Metab. 2025 Apr 10:dgaf223. Online ahead of print.
doi: 10.1210/clinem/dgaf223. PMID: 40208111.

Brief summary: This international multicenter study included 310 individuals with 46,XY partial gonadal dysgenesis (PGD) and 100 individuals with complete gonadal dysgenesis (CGD). Most PGD individuals assigned male underwent spontaneous puberty, and over half reached full pubertal development without hormone therapy.

This registry-based study offers important clinical insight into the broad phenotypic spectrum and pubertal trajectories of individuals with 46,XY partial gonadal dysgenesis. Among PGD patients raised male, 80% experienced spontaneous pubertal onset and 59% reached Tanner stage G5 without hormonal induction, indicating substantial endogenous androgen production. Additionally, spontaneous virilization during puberty occurred in 42% of PGD individuals initially raised female, highlighting the importance of reassessing sex assignment and treatment planning during adolescence.

Predictors of spontaneous pubertal progression included the presence of labioscrotal gonads and a positive testosterone response to HCG stimulation, both of which may serve as useful clinical biomarkers for individualized prognosis (2). These findings support a more conservative, phenotype-driven approach to management in some PGD cases, contrasting with historical trends toward early gonadectomy and hormone replacement.

Importantly, the study also confirms the substantial risk of gonadal tumor development, especially among PGD females (19.7%) and PGD males (8.8%), reinforcing the need for ongoing surveillance. Delayed puberty occurred in 18% of PGD females, emphasizing that pubertal outcomes are variable and cannot be predicted solely by karyotype or initial phenotype.

This study strengthens the case for individualized longitudinal care in PGD, balancing the benefits of spontaneous puberty against the oncologic risks of retained dysgenetic gonads.

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7.8. Association between pubertal timing and bone and body composition in young adult men

Antonio L, Priskorn L, Holmboe SA, Nordkap L, Bang KA, Juul A, Vanderschueren D, Jørgensen N

Sci Rep. 2025 Mar 19;15(1):9506.

doi: 10.1038/s41598-025-93895-5. PMID: 40108242.

Brief summary: This cross-sectional observational study, involving 2,056 healthy young Danish men, showed that those who experienced later pubertal voice break had lower lumbar bone mass and a leaner body composition. In contrast, earlier puberty timing was associated with higher bone density but minimal difference in body composition.

Pubertal timing influences long-term health outcomes, including bone density and body composition (1). While early or late puberty has been linked to various adult health risks, its impact on skeletal and muscular development in young men remains underexplored. This study assessed whether self-reported timing of voice break (a late pubertal milestone) correlates with bone and body composition in healthy young adult men.

In a cohort of 2,056 Danish men (median age 19), those reporting earlier voice break had higher lumbar and total body bone mineral density (BMD), but no difference in body composition, aside from slightly higher BMI and trunk fat mass. Conversely, men with later voice break had lower lumbar bone mineral content, bone area, and volume, although BMD was similar. They also had lower BMI, lean mass, and fat mass, resulting in a lower fat-to-muscle ratio and a relatively leaner body composition. These associations persisted after adjusting for age, BMI, lifestyle, and hormonal factors.

Physiological variation in pubertal timing is associated with measurable differences in bone and body composition in young adulthood. Early puberty correlates with higher BMD, while late puberty is linked to a leaner body profile and lower bone mass, suggesting that pubertal timing may influence peak bone mass acquisition and metabolic health trajectories.

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Basic Research

7.9. Central lipid sensing pathways contribute to the control of puberty and its alterations in conditions of obesity

Rodríguez-Vázquez E, Aranda-Torrecillas Á, López-Sancho M, Jiménez-Puyer M, Daza-Dueñas S, Barroso A, Sobrino V, Gaytan F, Obis E, Castellano JM, Tena-Sempere M

Am J Physiol Endocrinol Metab. 2025 May 1;328(5):E675-E694.

doi: 10.1152/ajpendo.00493.2024. PMID: 40172224.

Brief summary: This study highlights the involvement of brain lipid sensing pathways in the central regulation of puberty, depending on pubertal maturation stages and nutritional conditions.

Hypothalamic lipid-sensing pathways are central regulators of energy homeostasis. Among the central circuits controlling energy homeostasis, hypothalamic lipid sensing pathways, involving free fatty-acid receptors (FFARs), peroxisome proliferator-activated receptors (PPARs), and the bile-acid (BA) receptor, Takeda G protein-coupled receptor 5 (TGR5), have been recognized as major players, with putative roles in obesity and its

complications. However, their contribution to pubertal regulation and obesity-induced pubertal alterations remains largely unexplored(1,2), and the specific role of brain lipid-sensing pathways in the metabolic control of puberty remains poorly characterized.

The authors identified 299 lipid species differentially expressed in the mediobasal hypothalamus of female rats, depending on pubertal maturation or nutritional status (lean vs. early overfed). These lipid species were categorized into fatty acyls, glycerolipids, sterol lipids, and glycerophospholipids. Hypothalamic mRNA expression of various lipid-sensing receptors changed progressively during pubertal maturation: *Ffar2*, *Ffar3*, and *Lpl* expression decreased, while *Pparg* expression increased with pubertal maturation. Obesity was associated with increased mRNA expression of *Ffar2* and *Gpr84*, and decreased expression of *Lpl* at the time of pubertal onset.

Using fluorescence-activated cell sorting (FACS), expression of *Gpr84*, *Ppara*, *Lpl*, and *Cd36* was detected in Kiss1 neurons from both the arcuate nucleus (ARC) and the anteroventral periventricular nucleus (AVPV) of the hypothalamus. Notably, *Tgr5* expression was restricted to Kiss1 neurons in the ARC. Under conditions of obesity, *Gpr84* and *Lpl* mRNA levels were increased in ARC Kiss1 neurons at PND 32 (peripubertal), while in the AVPV, obesity had a more limited effect, illustrated by suppression of *Lpl* mRNA levels at PND 25 only (prepubertal).

Central blockade of *Gpr84* during pubertal transition did not affect pubertal onset in either lean or obese females. In contrast, central blockade of *Pparg/a* delayed pubertal timing in lean females but not in obese ones. Furthermore, central activation of *Tgr5* prevented the advancement of puberty in obese female rats.

This study highlights a novel role for brain lipid-sensing pathways in the regulation of puberty by nutritional status. The findings reveal differential involvement of central FFAR, PPAR, and TGR5 signalling depending on maturational stage and the presence of early-onset obesity.

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7.10. Dietary availability acutely influences puberty onset via a hypothalamic neural circuit

Goto T, Hagihara M, Irie S, Abe T, Kiyonari H, Miyamichi K

Neuron. 2025 Apr2;113(7):1036-1050.e5.
doi: 10.1016/j.neuron.2025.01.015. PMID: 39999843.

Brief summary: This study demonstrates how Agouti-related protein (AgRP)-expressing neurons in the arcuate nucleus (ARC), key hunger sensors, modulate the activity of ARC kisspeptin-expressing neurons (ARC^{Kiss} neurons), thereby influencing the regulation of puberty onset and reproductive function.

ARC Kiss neurons play a crucial role in puberty initiation by stimulating the release of gonadotropin-releasing hormone (GnRH). AgRP neurons, also located in the ARC, respond to signals of energy deficit, such as fasting, and conversely, are inhibited by signals of energy abundance, like leptin and insulin (1). Consequently, they could be the link between food availability and the initiation of puberty.

The authors used fiber photometry and calcium imaging in freely moving juvenile mice to investigate the dynamic relationship between ARC^{Kiss}neuron activity and ARC^{AgRP}neuron activity under various nutritional conditions.

In adult mice, ARC^{Kiss} neurons exhibit pulsatile calcium activity known as synchronous episodes of elevated Ca^{2+} (SEs^{Kiss}). These SEs^{Kiss} emerge a few days before the onset of puberty (marked by vaginal opening at postnatal day [PND] 35) in normally nourished female mice, consistent with their proposed role in triggering pubertal initiation. Peripubertal food restriction reduces the frequency of SEs^{Kiss} and delays pubertal

development, as evidenced by delayed vaginal opening and first estrus. Remarkably, restoring food availability after a period of restriction rapidly increases SEs^{Kiss} frequency within hours and rescues pubertal progression.

To uncover the underlying mechanisms, the authors examined whether ARC^{Kiss}neurons receive monosynaptic inhibitory input that is activated during starvation and relieved by feeding. ARC^{Agrp} neurons meet these criteria: they are GABAergic, responsive to nutritional status, and form monosynaptic connections with ARC^{Kiss} neurons, positioning them as plausible mediators of metabolic signals.

Activation of ARC^{Agrp} neurons suppresses the maturation of SEs^{Kiss} activity in ARC^{Kiss} neurons, in part in a body weight–dependent manner, thereby affecting pubertal onset and development. Conversely, inhibition of ARC^{Agrp} neurons under conditions of chronic food restriction partially restores SEs^{Kiss} frequency, which may support the occurrence of vaginal opening and the development of antral follicles.

In conclusion, Goto *et al*. propose a neural circuit that links energy balance to reproductive timing, wherein hunger-sensing ARC^{AgRP} neurons influence the emergence of pulsatile activity in kisspeptin neurons. However, previous studies suggest that the regulation of pubertal onset by nutritional cues is more complex, likely involving additional parallel pathways operating at different stages of pubertal development(2).

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7.11. Lifelong impacts of puberty timing on human plasma metabolic profiles: a metabolome-wide Mendelian randomization study

Zengjun L, Xuechao L, Si F, Dong L, Fei L, Cairong Z, Jian Z

Diabetes Obes Metab. 2025 Jan;27(1):184-195.
doi: 10.1111/dom.16000. PMID: 39402736

Brief summary: This Mendelian randomization (MR) study used data from over 329,000 women to investigate the association between puberty timing and adult plasma metabolomic profiles.

Timing of puberty has been associated with cardiometabolic outcomes (1, 2, 3), but causality remains uncertain due to confounding factors. This study addressed this question by examining the lifelong metabolic consequences of puberty timing. Genome-wide association study (GWAS) summary statistics on age at menarche (AAM) were extracted from the ReproGen Consortium ($n = 329{,}345$) (4), and associations with 174 plasma metabolites from 7 biochemical categories were tested in up to 86,507 individuals (5). Two-sample MR, two-step MR and multivariable Mendelian randomization (MVMR) were applied to assess both direct and mediated effects (6).

The authors found moderate evidence for causal relationships between puberty timing and 23 plasma metabolites, including 7 acylcarnitines, 8 amino acids, 2 biogenic amines, and 6 lysophosphatidylcholines. 16 associations remained robust after adjusting for childhood adiposity and birth weight. Two-step MR analysis suggested that many effects were mediated by adult adiposity, while MVMR analysis showed a moderate independent causal effect of puberty timing on 10 metabolites. Several of these metabolites are known to be associated with cardiovascular disease (7).

In conclusion, this study provides indication that puberty timing influences specific plasma metabolites, with part of this effect mediated by adult adiposity.

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7.12. Genetic links between ovarian ageing, cancer risk and de novo mutation rates

Stankovic S. *et al*
Nature. 2024 Sep;633(8030):608-614.
doi: 10.1038/s41586-024-07931-x. PMID: 39261734.

Brief summary: This study analysed UK Biobank data to expand current knowledge on the genetic architecture of ovarian ageing. It identified a shared genetic mechanism linking the start and end of female reproductive life, with *ZNF518A* emerging as a key regulator of both puberty timing and ovarian ageing.

Ovarian ageing, marked by age at natural menopause (ANM), impacts fertility and long-term health (1). While common genetic variants have been linked to ANM, the role of rare protein-coding variants was less explored (1). This study investigated rare damaging variants in over 100,000 women from the UK Biobank to uncover novel genetic contributors to ovarian ageing and their broader implications.

The study identified 9 genes associated with ANM, including 5 novel ones: *ETAA1*, *ZNF518A*, *PNPLA8*, *PALB2*, and *SAMHD1*. Notably, protein-truncating variants (PTVs) in *ZNF518A* led to shorter reproductive lifespan with earlier menopause (5.6 years) and later age at menarche (0.56 years), while damaging variants in *SAMHD1* delayed menopause by 1.35 years. Several of these genes are involved in DNA damage repair, reinforcing the link between genomic integrity and reproductive lifespan. Additionally, *SAMHD1* variants were associated with increased cancer risk in both sexes, particularly hormone-sensitive cancers.

Using data from the 100,000 Genomes Project, the authors also found that genetic predisposition to earlier menopause correlates with higher rates of maternally derived de novo mutations (DNMs) in offspring, although this was not replicated in the deCODE cohort.

This study expands the genetic architecture of ovarian ageing by identifying rare coding variants with large effects on ANM. It highlights the dual role of DNA damage repair genes in reproductive ageing and cancer susceptibility and suggests a potential intergenerational impact via increased DNMs. These findings offer new insights into the biology of reproductive ageing and its broader health consequences, with implications for fertility treatment and cancer risk assessment.

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8. Adrenals

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Introduction

For this year's chapter on 'Adrenals', we searched PubMed for articles on 'adrenal' or 'steroidogenesis' published in English between June 1, 2024 and July 31, 2025. This yielded more than 7,000 citations. We have examined all citations individually and selected the following collection of clinical and basic research articles. Whenever possible, we have avoided topics that have been discussed in the Yearbook 2024, unless progress in the field has been incremental. Emerging themes for this year's chapter include:i) SKA2 enhances stress-related glucocorticoid receptor signaling through FKBP4–FKBP5 interactions in neurons; ii) Cortisol awakening response prompts dynamic reconfiguration of brain networks in emotional and executive functioning; iii) Gut microbiota regulates stress responsivity via the circadian system; iv) International consensus statement on the diagnosis and management of pheochromocytoma and paraganglioma in children and adolescents; v) 17α-Hydroxylase/17,20-lyase Deficiency (17-OHD): A Meta-analysis of Reported Cases; vi) Prevalence of adrenal rest tumors and course of gonadal dysfunction in men with Congenital Adrenal Hyperplasia; and vii) Immunophenotypic implications of reverse-circadian glucocorticoid treatment in Congenital Adrenal Hyperplasia.

Mechanism of the Year

8.1. SKA2 enhances stress-related glucocorticoid receptor signaling through FKBP4-FKBP5 interactions in neurons

Hartmann J, Klengel C, Dillmann LJ, Hisey EE, Hafner K, Shukla R, SolivaEstruch M, Bajaj T, Ebert T, Mabbott KG, Rostin L, Philipsen A, Carlezon WA Jr, Gisabella B, McCullumsmith RE, Vergis JM, Klengel T, Berretta S, Daskalakis NP, Pantazopoulos H, Gassen NC, Ressler KJ

Proc Natl Acad Sci USA. 2024;121(52): e2417728121.
doi: 10.1073/pnas.2417728121

Brief summary: This *in vitro* and *in vivo* study highlights the role of SKA2 in the regulation of glucocorticoid receptor (GR) signaling within the central nervous system (CNS), hypothalamic-pituitary-adrenal (HPA) axis function and the stress response, and suggests potential targets for therapeutic intervention of stress-related psychiatric disorders.

Comment: Genes involved in the regulation of the HPA axis, including the *GR*, are associated with various stress-related psychopathologies, such as posttraumatic stress disorder (PTSD), major depressive disorder (MDD), and bipolar disorder (BD) (1-5). The cell cycle gene *SKA2*, encoding the spindle and kinetochore

associated (SKA) complex subunit 2, has been identified as a GR-interacting protein, enhancing the receptor's nuclear translocation in peripheral cells *in vitro* (6). SKA2 is a multifunctional scaffolding protein involved in cell cycle regulation, secretory autophagy, as well as GR signaling in peripheral cells. This study examined the precise roles of SKA2 in stress and GR signaling in the brain, and its involvement in HPA axis regulation.

Using diverse *in vitro* cell assays, the authors demonstrated that SKA2 is expressed throughout the mouse brain including the prefrontal cortex (PFC), periventricular nucleus (PVN), hippocampus and amygdala, associates with GR and acts as a positive regulator of GR signaling. SKA2 promotes GR signaling in neuronal cells through enhanced interaction with FKBP4, a cochaperone known to positively regulate GR function and in opposition to FKBP5, which leads to dissociation of FKBP5 from the complex. Furthermore, knocking down of Ska2 in the PVN of mice alters stress-induced HPA axis activity and delays its negative feedback loop of the HPA axis, which is pivotal in the regulation of stress response, and is often impaired in stress-related disorders. Moreover, SKA2 expression is increased in postmortem human hippocampus and amygdala from individuals with BD, and SKA2 expression may follow a diurnal rhythm, which is shifted and less pronounced in people with BD than healthy controls.

In conclusion, these findings highlight the role of SKA2 in the regulation of GR signaling within the CNS, HPA function and the stress response, provide further insight into the molecular basis of stress-related psychiatric disorders, and suggest potential targets for therapeutic intervention.

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New Mechanisms

8.2. Cortisol awakening response prompts dynamic reconfiguration of brain networks in emotional and executive functioning

Zeng Y, Xiong B, Gao H, Liu C, Chen C, Wu J, Qin S

Proc Natl Acad Sci USA. 2024;121(52):e2405850121.
doi: 10.1073/pnas.2405850121

Brief summary: This prospective, case control study shows that the cortisol awakening response (CAR) proactively tunes large scale brain network dynamics to optimize emotional discrimination and working memory, underlining its critical role in human adaptive cognition.

Comment: As a hallmark of human endocrine activity, the cortisol awakening response (CAR), i.e. the natural rise in cortisol concentrations shortly after waking, plays a critical role in proactively modulating emotional and executive functions (1-7). This study investigated how the CAR affects the brain's dynamic reconfiguration and supports emotional and executive functions. While CAR is thought to play a proactive role in preparing the brain for daily challenges, the underlying neural mechanisms have not been delineated.

The authors investigated large-scale brain networks involved in emotional and executive functions in 122 male volunteers; 62 participants (mean age: 22.9 years; range: 18 to 27 years) in Cohort 1 and 60 participants in Cohort 2 (21.6 years; 20 to 24 years). Participants were given low dose dexamethasone (DXM, 0.5 mg) to suppress CAR, or placebo, the night before fMRI scans. The next afternoon, they performed 3 tasks: rest, emotional discrimination, and 2 back working memory (WM), while fMRI data were analyzed using a hidden Markov model (HMM) to identify transient "brain states" across 14 large scale networks.

In terms of behavior, suppression of CAR selectively impaired emotional discrimination performance without affecting WM. Conversely, participants with robust CAR levels showed better performance across both tasks. Furthermore, CAR suppression reduced both the fractional occupancy (how often a network state is active) and mean lifetime of task relevant brain states during emotion and WM tasks. Using information theoretic measures, the authors found that lower CAR increased transition complexity, i.e., less efficient shifting, among visual sensory and salience anchored states during emotional tasks. Interestingly, the opposite pattern appeared during the WM task, where complexity decreased among executive control and visuospatial networks.

These findings show that CAR shapes the brain's ability to dynamically allocate resources to emotional and executive processing. CAR elevates both the frequency and stability of functionally specialized brain states and refines the complexity of state-to-state transitions in a task-specific manner. By establishing a causal link between CAR and brain network dynamics, this study presents a neuroendocrine mechanism for how cortisol prepares the mind for daily emotional and cognitive demands. Furthermore, it provides evidence that the CAR proactively tunes large scale brain network dynamics to optimize emotional discrimination and working memory, underlining its critical role in human adaptive cognition. However, this study has several limitations. First, it focused on CAR in males to avoid the confounding effect of female menstrual cycles, so may not be generalizable to females. Furthermore, it did not include concurrent measures of physiologic activity and task-induced transient modulators that may interplay with CAR. Future studies with optimal design and innovative neuroimaging techniques are required to address the mechanisms underlying time-dependent effects of CAR in the morning and in the afternoon.

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8.3. Gut microbiota regulates stress responsivity via the circadian system

Tofani GSS, Leigh SJ, Gheorghe CE, Bastiaanssen TFS, Wilmes L, Sen P, Clarke G, Cryan JF

Cell Metab. 2025; 37(1): 138-153.e5. PMID: 39504963

doi: 10.1016/j.cmet.2024.10.003.

https://pubmed.ncbi.nlm.nih.gov/39504963/

Brief summary: This *in vitro* and *in vivo* animal study provides compelling evidence that gut microbiota modulation of stress responsiveness exhibits diurnal rhythmicity.

Comment: Stress and circadian systems are interconnected through the hypothalamic-pituitary-adrenal (HPA) axis to maintain responses to external stimuli. In addition to playing a central role in both stress and circadian signaling, the HPA axis is one of the key pathways through which the gut microbiota can shape brain function and behavior (1). The trillions of microorganisms that reside in the gut have co-evolved with their hosts, resulting in an intertwined relationship between the gut microbiota and host physiology (2). Stress-induced glucocorticoid release is modulated by the gut microbiota because germ-free (GF) mice display exaggerated glucocorticoid levels following stress that can be recovered upon colonization (3). In addition, the gut microbiome displays strong diurnal oscillations in composition and metabolic output that are important to maintain metabolic health (4-6), while microbial depletion leads to altered baseline levels of glucocorticoids at different times of the day (7). There is evidence that gut microbes regulate brain function, the stress response and circadian rhythms. However, the mechanisms how these signals are orchestrated remain unknown.

Conducted in germ-free mice with comprehensive bioinformatic analyses of transcriptomic and metabolomic data, this study shows that altering the gut microbiota disrupts diurnal oscillations in stress- and circadian-related pathways across key brain regions involved in both circadian regulation and the behavioral stress response. One of these regions, the suprachiasmatic nucleus, maintains glucocorticoid rhythms; the results show that gut microbiota-driven circadian disruption alters the diurnal pattern of circulating corticosterone.

These findings have significant implications. They reveal that diurnal rhythmicity is essential to how the gut microbiota regulates the stress response, providing the first clear evidence that the microbiota, circadian system, and stress axis operate in an integrated, time-dependent manner. Since glucocorticoids influence multiple physiological systems, including immunity and metabolism, the findings of this study deepen our understanding of microbe-host interactions. Given that many stress-related disorders involve disruptions in both circadian rhythms and gut microbiota and are exacerbated by modern lifestyle stressors, this work underscores the potential for microbiota-targeted interventions. Notably, the identification of *Limosilactobacillusreuteri* as a circadian-sensitive strain opens new avenues for developing time-specific treatments for stress-related conditions.

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Important for Clinical Practice

8.4. International consensus statement on the diagnosis and management of phaeochromocytoma and paraganglioma in children and adolescents

Casey RT, Hendriks E, Deal C, Waguespack SG, Wiegering V, Redlich A, Akker S, Prasad R, Fassnacht M, Clifton-Bligh R, Amar L, Bornstein S, Canu L, Charmandari E, Chrisoulidou A, Freixes MC, de Krijger R, de Sanctis L, Fojo A, Ghia AJ, Huebner A, Kosmoliaptsis V, Kuhlen M, Raffaelli M, Lussey-Lepoutre C, Marks SD, Nilubol N, Parasiliti-Caprino M, Timmers HHJLM, Zietlow AL, Robledo M, Gimenez-Roqueplo AP, Grossman AB, Taïeb D, Maher ER, Lenders JWM, Eisenhofer G, Jimenez C, Pacak K, Pamporaki C

Nat Rev Endocrinol. 2024; 20(12): 729-748.

PMID: 39147856 doi: 10.1038/s41574-024-01024-5.

https://pubmed.ncbi.nlm.nih.gov/39147856/

Brief summary: This article presents newinternational guidelines on Pheochromocytomas and Paragangliomas.

Comment: Phaeochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumors arising from the adrenal medulla or extra-adrenal sympathetic and parasympathetic paraganglia. PPGL are more frequently diagnosed in adult than in pediatric populations; pediatric cases account for only 10–20% of all detected cases of PPGL with an estimated annual incidence of 0.5–2.0 per million children (1). Due to the slow-growing nature of the tumors and usual delays in diagnosis, the true prevalence of PPGL in childhood is likely to be much higher than currently estimated. The median age at presentation is 11–15 years (2, 3) and PPGL are exceedingly rare in children under 5 years of age.

Up to 70–80% of childhood PPGL are hereditary, accounting for a higher incidence of metastatic and/or multifocal PPGL in pediatric patients than in adult patients (4). Key differences in the tumor biology and management, together with rare disease incidence and therapeutic challenges in pediatric compared with adult

patients, mandate close expert cross-disciplinary teamwork. Teams should ideally include adult and pediatric endocrinologists, oncologists, cardiologists, surgeons, geneticists, pathologists, radiologists, clinical psychologists and nuclear medicine physicians. This Consensus Statement serves as a catalyst to further promote close working relationships between pediatric and adult specialists managing patients with PPGL, and between specialists and national and international patient support and advocacy groups.

This International Consensus Statement highlights the strong hereditary basis of PPGL and the need for surveillance of asymptomatic genetic carriers from childhood or early adulthood and for lifelong follow-up. In addition, it supports a role for wide-scale adoption of 'family clinic' models for families affected by PPGL or families with individuals carrying a PPGL predisposition gene. Finally, this international and collaborative work emphasizes the need for novel treatment options and the need for children and young adults to be included in local, national and international data registries of PPGL and in the design of clinical trials.

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8.5. 17α-hydroxylase/17,20-lyase deficiency (17-ohd): a meta-analysis of reported cases

Willemsen AL, Torpy DJ, De Sousa SMC, Falhammar H, Rushworth RL

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PMID: 39500362 doi: 10.1210/clinem/dgae773.
https://pubmed.ncbi.nlm.nih.gov/39500362/

Brief summary: This meta-analysis examined the relationship between *CYP17A1* genotype and clinical presentation in a global cohort.

Comment: 17α-hydroxylase/17,20-lyase deficiency (17-OHD) accounts for only 1% of all cases of CAH. This enzyme catalyzes 2 distinct steps in steroidogenesis: 17α-hydroxylation of pregnenolone and progesterone to 17α-hydroxylated products and 17,20-bond cleavage of these products to the C19 androgen precursors, dehydroepiandrosterone and androstenedione (1-4). Homozygous pathogenic variants in *CYP17A1* disrupt activity of the steroidogenic enzymes 17α-hydroxylase/17,20-lyase, resulting in the clinical syndrome of 17-OHD characterized by hypertension, hypokalemia, and disorders of sexual development. Pathogenic variants in *CYP17A1* lead to complete or partial loss of enzymatic activity and clinical presentations of varying severity (5-8). This study examined the relationship between *CYP17A1* genotype and clinical presentation in a global cohort.

The authors searched PubMed and Scopus for case reports and cohort studies published between 1988 and 2022 reporting clinical data on patients with 17-OHD. Of 451 studies, 178 met inclusion criteria comprising a total of 465 patients. They pooled patient data and examined associations between causative variants and their clinical presentations. There were 465 unique patients with mean age 18.9 (SD: 9.0) years, 52.5% ($n=244$) were XY and 6.4% ($n=29$) were phenotypically male. Common clinical presentations were hypertension (57.0%, $n=256$), hypokalemia (45.4% $n=211$), primary amenorrhea (38.3%, $n=178$), cryptorchidism (15.3%, $n=71$), and atypical genitalia (14.2%, $n=66$). Homozygous variants were seen in 48.0% ($n=223$) of patients. Frequently occurring variants included p.Y329Kfs ($n=86$), p.D487_F489del ($n=44$), and p.W406R ($n=39$). More severe variants, such as p.Y329Kfs, were associated with hypocortisolism ($P<0.05$), combined hypokalemia and hypertension ($P<0.01$), and disordered sexual development ($P<;0.01$).

In conclusion, 17-OHD is a rare, frequently misdiagnosed disease. Males are typically diagnosed earlier because of ambiguous genitalia associated with less severe variants, whereas females are typically diagnosed later because of primary amenorrhea and hypertension. Patients presenting with disordered sexual development and hypertension should be investigated for 17-OHD.

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8.6. Prevalence of adrenal rest tumors and course of gonadal dysfunction in a clinical sample of men with congenital adrenal hyperplasia: a longitudinal analysis over 10 years

Auer MK, Büyükerzurmulu D, Lottspeich C, Bidlingmaier M, Rieger E, Nowotny H, Tschaidse L, Auchus RJ, Reisch N

Eur J Endocrinol. 2024; 191(3): 370-380. PMID: 39308408

doi: 10.1093/ejendo/lvae112.

https://pubmed.ncbi.nlm.nih.gov/39308408/

Brief summary: This longitudinal, retrospective single-center study evaluated testicular adrenal rest tumors (TART) and gonadal function in 27 adult men with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency.

Comment: TART were present in 11 participants. Subnormal testosterone concentrations were frequent in both groups (43% without TART; 55% with TART), but testosterone and luteinizing hormone (LH) concentrations increased modestly over time in both cohorts; with TART, testosterone from 10.1 to 17.3nmol/l; without TART, testosterone from 10.3 to 12.8 nmol/l. Men with TART had slightly higher adjusted testosterone concentrations compared to those without (14.0 nmol/l vs 11.9 nmol/l). Glucocorticoid dose decreased marginally over time. Importantly, inhibin B concentrations declined in men with large TART, despite no change in TART size, suggesting Sertoli cell dysfunction and potential fertility impairment. This decline occurred independently of adrenal androgen control, testosterone trends, or glucocorticoid dose.

These findings suggest that while TART do not lead to progressive testosterone deficiency, gonadal dysfunction remains prevalent in men with CAH. Routine imaging for TART in asymptomatic adults may not be necessary. However, monitoring fertility markers, especially inhibin B, is recommended in men with large or persistent TART. This highlights the importance of individualized monitoring of gonadal function and fertility potential in men with CAH, with a focus on balancing hormonal control and minimizing overtreatment (1, 2).

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8.7. The endocrine phenotype induced by pediatric adrenocortical tumors is age- and sex-dependent

Kunstreich M, Dunstheimer D, Mier P, Holterhus PM, Wudy SA, Huebner A, Redlich A, Kuhlen M

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PMID: 38318871 doi: 10.1210/clinem/dgae073.

https://pubmed.ncbi.nlm.nih.gov/38318871/

Brief summary: This retrospective study investigated the endocrine manifestations in 155 pre- and pubertal children and adolescents with adrenocortical tumors included in the German Paediatric Oncology Haematology-Malignant Endocrine Tumour (GPOH-MET) studies during 1997-2022.

Comment: Adrenocortical carcinomas are rare in children and most adrenocortical tumors (ACT) are functional (1-3). This study investigated the endocrine manifestations in 155 pre-and pubertal children and adolescents with ACT included in the GPOH-MET study (cases from Germany, Austria, Switzerland) during 1997-2022. Median age at diagnosis was 4.2 years with a female preponderance (71%) and the median time interval of symptoms prior to diagnosis was 4.2 months.

In prepubertal girls ($n=63$) the main symptoms were pubarche (68.3%), clitoral hypertrophy (49.2%) and weight gain (31.7%) while as many as 12.7% of the girls did not have any clinical signs or symptoms. In pubertal girls ($n=47$) the main manifestations were excessive pubic hair (46.8%), acne (36.2%) and hypertension (36.2). In addition, 25% of the pubertal females presented with abdominal/back pain. In prepubertal boys ($n=34$) the leading signs and symptoms were pubarche (55.9%), penile growth (47.1%) and acne (32.4%), while the pubertal boys ($n=11$) mostly presented with weight gain (45.5%), hypertension (36.4%) and excess pubic hair/Cushingoid features (27.3%). Half of the pubertal boys also complained of back pain.

The most frequent symptoms in patients of prepubertal age with adrenocortical adenoma (ACA) were pubarche (56.7%), weight gain/obesity (40.0%), and clitoral hypertrophy/penile growth (33.3%), whereas pubarche (72.5%), clitoral hypertrophy/penile growth (56.9%), and acne (31.4%) were most frequent in patients with adrenocortical carcinoma (ACC). In pubertal patients with ACA, the most frequent symptoms were excessive pubic hair (47.1%), weight gain/obesity (29.4%), and sweat odor or deep voice (23.6%), while in patients with ACC, the most frequent symptoms were hypertension (50.0%), excessive pubic hair (42.1%), and weight gain/obesity and tiredness (39.5%).

In metastatic disease, the most frequent sign was hypertension, while in those without metastasis the most common sign was clitoral hypertrophy. In addition, no differences were observed for endocrine manifestations in ACC patients with Ki67-index $<$ 15% compared to Ki67-index $\geq$ 15%. The hormonal profiles were mostly in line with the endocrine manifestations, but Cushing's syndrome was overlooked in several cases, especially in prepubertal children with androgen excess.

In conclusion, this is the first comprehensive analysis of the various endocrine manifestations in 155 children and adolescents with ACT. The latency from first endocrine symptoms to ACT diagnosis was 4.8 months, which concurs with previous reports. These data demonstrate that the endocrine phenotype is age- and sex-dependent, and it is not associated with tumor dignity. The most frequent overarching endocrine phenotype is mixed (virilization/peripheral precocity combined with Cushing syndrome; 53.8%), followed by virilization/peripheral precocity (27.9%), and Cushing syndrome (11.5%).

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8.8. 46,XX males with congenital adrenal hyperplasia: a clinical and biochemical description

Adriaansen BPH, Utari A, Westra D, Juniarto AZ, Ariani MD, Ediati A, Schröder MAM, Span PN, Sweep FCGJ, Drop SLS, Faradz SMH, van Herwaarden AE, Claahsen-van der Grinten HL

Front Endocrinol (Lausanne). 2024; 15:1410122.

PMID: 39175568 doi: 10.3389/fendo.2024.1410122.

https://pubmed.ncbi.nlm.nih.gov/39175568/

Brief summary: This observational cohort study investigated 9 untreated Indonesian 46,XX individuals with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) ($n=6$) and 11-hydroxylase deficiency (11OHD) ($n=3$), who were reared as males. Despite markedly low cortisol concentrations, all patients survived without glucocorticoidtreatment and displayed androgen profiles within the normal male reference range.

Comment: This study presents a rare clinical and biochemical characterization of 9 untreated 46,XX individuals with CAH who were raised as males, highlighting the complex balance between androgen excess and cortisol deficiency. A particularly novel aspect is the quantification of 11-oxygenated androgens, which comprise a significant portion of the androgen pool and contribute to virilization. These patients displayed adrenal androgen concentrations within the male reference range and maintained a stable male phenotype during adolescence and adulthood. These findings indicate that these androgens have comparable receptor activity to testosterone and play an essential role in CAH pathophysiology (1).

Remarkably, despite all patients having extremely low cortisol concentrations and elevated ACTH baseline concentrations, with no meaningful cortisol response to ACTH stimulation, most did not experience clinical signs of adrenal insufficiency beyond early childhood. This clinical stability may be attributed to the compensatory activity of steroid precursors, such as 21-deoxycortisol and 11-deoxycortisol, which exhibit approximately 49% and 15% of cortisol's biological activity on glucocorticoid receptors, respectively (2). However, this outcome must be interpreted with caution due to potential survival bias; only those who remained clinically stable without treatment are represented, potentially excluding more severe cases.

Current approaches emphasize delaying genital surgery and prioritizing shared decision-making in 46,XX patients with CAH, as male-reared individuals can establish a stable male gender identity and good quality of life (3). Clinically, the study underscores the dilemma in managing 46,XX CAH individuals reared as males, where conventional glucocorticoid therapy, while protective against adrenal crisis, may disrupt the established gender identity by reducing androgen concentrations and triggering feminization. This study highlights the importance of an individualized therapeutic approach, combined with culturally sensitive counseling, in such cases.

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Clinical Trials – New Treatments

8.9. Adrenal suppression from vamorolone and prednisone in Duchenne muscular dystrophy: results from the phase 2b clinical trial

Ahmet A, Tobin R, Dang UJ, Rooman R, Guglieri M, Clemens PR, Hoffman EP, Ward LM

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doi: 10.1210/clinem/dgae521.

https://pubmed.ncbi.nlm.nih.gov/39097643/

Brief summary: This paper presents a *post-hoc* analysis of data from a randomized, double-blind, placebo- and prednisone-controlled 24-week trial of vamorolone with a 24-week crossover extension.

Comment: This study assessed the frequency of adrenal suppression induced by vamorolone and prednisone in pediatric Duchenne's muscular dystrophy (DMD) and cortisol concentrations thresholds using a monoclonal antibody immunoassay in patients with pediatric DMD. It was previously suggested that Vamorolone, with distinct chemical structure and differences in mechanism of action, may be a safer alternative to prednisone for treating DMD, offering similar anti-inflammatory efficacy (*via* the glucocorticoid receptor), with fewer side effects related to growth and bone health (1). Mechanistically, Vamorolone shows reduced positive gene transcriptional activity (transactivation) than corticosteroids but retains the inhibition of nuclear factor κB

proinflammatory pathways (transrepression), while it has been suggested that the lack of effect of modulatory 11β-hydroxysteroid dehydrogenase enzymes, explains the fewer corticosteroid-associated bone morbidities (2). In addition, Vamorolone is a potent antagonist of the mineralocorticoid receptor, with the potential to reduce cardiomyocyte pathology frequently seen in DMD (3). Therefore, a thorough evaluation of adrenal function in these patients both with various stimulated cortisol concentrations cut-offs and various Vamorolone doses as compared to standard prednisone (0.75 mg/kg/day) in pediatric DMD, is of clinical importance.

Indeed, this study showed that adrenal insufficiency after Vamorolone and prednisone was frequent; when associated with Vamorolone adrenal insufficiency appeared dose dependent. The authors recommend hydrocortisone stress dosing in patients receiving Vamorolone.

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8.10. Corticosteroid rhythms in hypoparathyroid patients

Astor MC, Løvås K, Methlie P, Simunkova K, Assmus J, Husebye ES

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doi: 10.1093/ejendo/lvae102.

https://pubmed.ncbi.nlm.nih.gov/39167533/

Brief summary: This paper reports a crossover intervention study of 10 patients with primary hyperparathyroidism and 10 healthy volunteers, matched for sex and age.

Comment: It is infrequently noted that in hypoparathyroidism, deficiency in parathyroid hormone (PTH) is associated with lower concentrations of both aldosterone and corticosteroids (cortisol and cortisone) in tissues (1). There is evidence that PTH increases the secretion of aldosterone from the adrenals directly, as well as indirectly by activating the renin–angiotensin system (2). Upregulation of aldosterone synthesis might contribute to the higher risk of arterial hypertension and of cardiovascular damage in patients with primary hyperparathyroidism (3). A direct relation between PTH secretion and adrenocortical secretion is supported by the observation that PTH stimulates both cortisol and aldosterone from human adrenocortical cells and by the high expression of PTH1R in zona glomerulosa (4).

In this study, adrenocortical hormone concentrations were reduced in postsurgical hypoparathyroidism and partly restored by short-term continuous subcutaneous PTH (1-34) therapy. Tissue aldosterone and cortisone concentrations were lower in hypoparathyroid patients than in healthy controls, with no difference in tissue cortisol, but a higher cortisol to cortisone ratio. The ratio of cortisol to cortisone was higher in hypoparathyroid patients, indicating a potential shift in how these hormones are processed (1). Despite the reduced concentrations, both circadian (day-night) and ultradian (shorter than a day) rhythms of cortisol, cortisone, and aldosterone were still present in hypoparathyroid patients. In addition, hypoparathyroid patients displayed both ultradian and circadian rhythmicity for tissue cortisol, cortisone, and aldosterone. When treated with PTH (1-34), hypoparathyroid patients showed increased tissue concentrations of aldosterone, cortisol, and a decrease in the cortisol to cortisone ratio, suggesting a restoration of normal hormone balance.

Understanding these rhythm alterations and the impact of PTH therapy is of clinical significance as it can help clinicians optimize treatment strategies for hypoparathyroidism and potentially improve patient outcomes.

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New Paradigms

8.11. Immunophenotypic implications of reverse-circadian glucocorticoid treatment in Congenital Adrenal Hyperplasia

Nowotny HF, Choi H, Ziegler S, Doll N, Bäuerle A, Welp AC, Dubinski I, Schiergens K, Neumann U, Tschaidse L, Auer MK, Rothenfusser S, Schmidt H, Reisch N

Int J Mol Sci. 2025;26(4):1479. PMID: 40003944
doi: 10.3390/ijms26041479.
https://pubmed.ncbi.nlm.nih.gov/40003944/

Brief summary: This study investigated the immunological effects of reverse-circadian glucocorticoid treatment compared to conventional circadian glucocorticoid regimens in patients with Congenital Adrenal Hyperplasia (CAH).

Comment: Management of classic CAH requires lifelong glucocorticoid and mineralocorticoid replacement to prevent adrenal crises and to control androgen excess. Standard treatment involves hydrocortisone (HC) given in 3 daily doses, with the highest in the morning to mimic the natural diurnal circadian rhythm (circadian treatment, CT). This approach aims to align with peak hypothalamic-pituitary-adrenal axis activity and minimize side effects. Alternatively, some centers prefer reverse-circadian treatment (RC), which sets higher evening doses to suppress the early morning hypothalamic-pituitary-adrenal surge. While much attention has been given to optimizing biochemical control, the broader physiological consequences of glucocorticoid replacement treatment remain insufficiently studied, particularly their effects on immune function. Glucocorticoids are critical regulators of immune activity, and disruptions in their circadian rhythm, whether endogenous or treatment-induced, can significantly alter immune phenotypes.

These authors investigated the immunological effects of RC therapy ($n = 16$) compared to conventional circadian glucocorticoid regimens, including standard HC and modified-release HC ($n = 38$), in a cohort of pediatric and adolescent patients with CAH. Immune cell phenotypes, cytokine profiles, and natural killer cell cytotoxicity were assessed.

Patients receiving RC therapy showed a lower percentage of $CD4^+CD25^+$ T cells. Following the transition to CT, there was a notable increase in non-classical monocytes and a decrease in Th17 cells. Additionally, RC therapy was associated with reduced CD107 expression and an elevated proportion of $NKp30^+$ natural killer cells. When comparing immune profiles before and after switching from RC to conventional CT therapy, patients previously on RC showed lower NKG2D expression. Both conventional and RC glucocorticoid regimens exerted distinct effects on immune function, with conventional treatment demonstrating modest advantages in normalizing immune phenotypes. Given that only 3 subjects received modified-release hydrocortisone (MRHC) treatment, no comparisons could be made between HC and MRHC groups.

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Reviews

8.12. Development of 24-hour rhythms in cortisol secretion across infancy: a systematic review and meta-analysis of individual participant data

Kervezee L, Romijn M, van de Weijer KNG, Chen BSJ, Burchell GL, Tollenaar MS, Tamayo-Ortiz M, Philbrook LE, de Weerth C, Cao Y, Rotteveel J, Eiden RD, Azar R, Bush NR, Chis A, Kmita G, Clearfield MW, Beijers R, Gröschl M, Wudy SA, Kalsbeek A, Mörelius E, Finken MJJ

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PMID: 39207206 doi: 10.1210/clinem/dgae590.
https://pubmed.ncbi.nlm.nih.gov/39207206/

Brief summary: This review investigated the development of 24-hour cortisol rhythmicity in infancy and demonstrated that a stable early-morning cortisol peak emerges by 6–9 months.

Comment: In adults, cortisol follows a daily rhythm, peaking in the early morning and dropping around midnight (1, 2). Hydrocortisone therapy for adrenal insufficiency aims to replicate this pattern. Incorrect dosing can lead to undertreatment, raising the risk of adrenal crises and, in patients with congenital adrenal hyperplasia, androgen excess or overtreatment, which increases the risk of obesity, high blood pressure, and insulin resistance (3). Inborn adrenal insufficiency typically presents shortly after birth, but infant dosing can be challenging due to uncertainty about when the normal cortisol rhythm is fully established.

These authors conducted an individual participant data meta-analysis of salivary cortisol concentrations in healthy infants to establish normative data and inform hydrocortisone dosing. By combining data from 15 cohorts, they found that a stable early-morning cortisol peak emerges by 6–9 months, supported by sensitivity analyses; cosinormodeling confirmed a clear 24-hour rhythm with a single morning peak in the second half of the first year.

The study enhances our understanding of hypothalamic-pituitary-adrenal (HPA) axis maturation. The authors recommend clinical trials to evaluate the long-term safety and efficacy of development-based hydrocortisone dosing before applying it in practice.

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8.13. Examining aldosterone plasma concentration alterations post-ACTH stimulation in healthy subjects: a systematic literature review and meta-analysis on ACTH's role in aldosterone secretion

Stathori G, Alexakis D, Chrousos GP, Paltoglou G
Hormones (Athens). 2024; 23(4):765-775.
PMID: 39052132 doi: 10.1007/s42000-024-00583-6.
https://pubmed.ncbi.nlm.nih.gov/39052132/

Brief summary: This systematic review and meta-analysis found a significant increase in plasma aldosterone concentrations in healthy subjects after ACTH stimulation, irrespective of the ACTH dose.

Comment: It is infrequently reported that ACTH, in addition to the renin-angiotensin-aldosterone system (RAAS), is a potent aldosterone stimulator. While RAAS is the primary regulator of aldosterone in normal physiological conditions, ACTH plays a crucial role in modulating this response, especially in the adrenal gland (1). The precise role of ACTH in RAAS is not fully elucidated. It has been shown that ACTH primarily regulates aldosterone production in the short term, particularly during acute stress or in conditions like primary aldosteronism (1).

These authors performed a systematic search of PubMed, Medline, and Google Scholar databases according to PRISMA guidelines and meta-analysis. The presented data indicate that even low doses of ACTH are adequate to stimulate aldosterone secretion. This suggests a potential contribution to conditions associated with increased ACTH concentrations on aldosterone secretion regulation beyond the renin-angiotensin-aldosterone axis. In addition, age-related differences in aldosterone plasma concentration alterations after ACTH stimulation have been reported (2). As the incidence of hypertension increases with age, the contribution of ACTH to aldosterone secretion in older subjects should be determined via further research. Establishing a normal aldosterone response threshold following standardized ACTH stimulation could aid in identifying individuals with ACTH-dependent aldosterone hypersecretion and guide personalized and effective treatment strategies.

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8.14. Circadian and ultradian rhythms: clinical implications

Lightman SL, Conway-Campbell BL

J Intern Med. 2024;296(2):121-138.

PMID: 38825772 doi: 10.1111/joim.13795.

https://pubmed.ncbi.nlm.nih.gov/38825772/

Brief summary: This review highlights the importance of rhythmic oscillations of glucocorticoid concentrations for maintaining optimal cognitive, metabolic, cardiovascular and immune functions.

Comment: In this review, the authors explain why rhythmic oscillations of glucocorticoids are essential for maintaining optimal cognitive, metabolic, cardiovascular, and immune functions. These oscillations ensure the continuous dynamic balance required for effective hormonal homeostasis. Disruptions to these rhythms, such as those caused by conventional glucocorticoid therapy, are associated with well-documented adverse effects on mood, appetite, and metabolic regulation. Drawing on both rodent and human studies, the authors emphasize the physiological importance of preserving natural hormone patterns. The review also highlights the shortcomings of current steroid therapies, which often fail to mimic these natural rhythms and suggests that the physiological hormone patterns of glucocorticoid treatment and hormone replacement should be a much higher priority for endocrinologists and the pharmaceutical industry. The review also discusses promising new technologies, such as 24-hour cortisol monitoring, that offer valuable tools for optimizing treatment and advancing personalized hormone replacement strategies.

Food for Thought

8.15. Increased prevalence of negative pregnancy and fetal outcomes in women with primary adrenal insufficiency: a systematic review and meta-analysis

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PMID: 39277840 doi: 10.1007/s12020-024-04023-8.

https://pubmed.ncbi.nlm.nih.gov/39277840/

Brief summary: This systematic review and meta-analysis evaluated the impact of maternal primary adrenal insufficiency (PAI) during pregnancy, due to either Addison disease (AD) or congenital adrenal hyperplasia (CAH), with data from PubMed/Medline, Cochrane/CENTRAL, and Google Scholar. A total of 31 studies were included for qualitative analysis and 11 for quantitative analysis.

Comment: Women with primary adrenal insufficiency (PAI) face an increased risk of negative pregnancy and fetal outcomes, including higher rates of miscarriage, preterm birth, and small for gestational age (SGA) babies (1). There is also an increased risk of adrenal crises during pregnancy, and while maternal mortality is uncommon, suboptimal management can be fatal (2).

This systematic review and meta-analysis found a higher prevalence of pregnancies with negative outcome (spontaneous abortion, preterm birth) and of negative fetal outcome (SGA) in women with either AD or CAH, compared with control pregnancies. Of note, the meta-analysis showed a mean prevalence of spontaneous abortion of 18% (18% and 17% in women with AD or CAH, respectively). The mean prevalence of preterm birth was 11% (13% and 9% in women with AD or CAH, respectively). The mean prevalence of SGA neonates was 8% (5% and 10% in women with AD or CAH, respectively). Mean fetal birth weight was within normal range in all women with PAI, as well as in women with AD or CAH.

Pregnancy with PAI can be successful, but it requires careful management and monitoring to mitigate the increased risks of adverse outcomes (3). A multidisciplinary approach, including specialized endocrine and obstetric care, is essential for optimizing both maternal and fetal well-being (3).

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9. Oncology and Chronic Disease

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Introduction

Recent data on childhood cancer survivors continue to highlight fertility preservation as a key focus area. Advances in fertility preservation methods and assisted reproduction have significantly improved reproductive outcomes compared to previous decades.

Additionally, the shift toward personalized antineoplastic therapies—tailored based on the patient's genetic profile and tumor gene expression—has contributed to better preservation of fertility.

Emerging preliminary evidence also suggests a link between specific gene polymorphisms and the risk of endocrine complications, especially gonadal damage.

Late Endocrine Toxicity of Cancer Therapy

9.1. The late effects of hematopoietic stem cell transplants in pediatric patients: a 25-year review

Lee SL, Nguyen QN, Ho C, James S, Kaur A, Lim A, Tiedemann K, Zacharin M
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PMID: 38534046. doi: 10.1210/clinem/dgae196.
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Brief summary: This single-center, retrospective study analysed long-term health outcomes of 228 5-year survivors of pediatric allogeneic hematopoietic stem cell transplant (HSCT), treated between 1985 and 2011.

Gonadotoxicity was more common in females and in those who received total body irradiation (TBI)-based conditioning. All 24 women who received 12 Gy TBI developed premature ovarian insufficiency (POI), compared to 17/28 conditioned with busulfan/cyclophosphamide (BuCy). 32 of 33 men exposed to TBI or testicular irradiation exhibited impaired spermatogenesis. All 5 males who received TBI had azoospermia vs 3/6 conditioned with chemotherapy. Preservation of gonadal function was associated with younger age at HSCT. Spontaneous pregnancies were reported by 8 of 37 sexually active females, resulting in 10 live births; 3 had received TBI, and 5 had a prior POI diagnosis 5–16 years before conception. Short stature was common, with GH axis disruption documented in 30% of patients. 84 of 94 patients exposed to thyroid radiation had ultrasound data available; 51% developed nodules (30% malignant) after a median of 12 years from irradiation and 26% developed hypothyroidism. Diabetes or prediabetes was diagnosed in 7% of patients; lipids (available in 116/228 patients) were abnormal in 50% of cases. Among the 183 patients with available BMI data, 20% were obese, 9% overweight, and 10% underweight. Hypertension was found in 22 of 109 patients, with 10 receiving treatment. Vitamin D status was available in 113 of 228 patients and was abnormal in 45 patients. 17 HSCT survivors had died, primarily due to subsequent malignant neoplasms.

Comment: Long-term follow-up data from this large Australian study confirm the well-known sequelae of HSCT and the detrimental effects of TBI. A limitation of the study is the lack of relevant data (including weight, BMI, blood pressure, lipids, hormones, vitamin D levels, and ultrasound) for a significant proportion of patients, due to its retrospective design. The finding of a significant percentage of transplanted women with spontaneous pregnancies after a diagnosis of POI, is surprising and likely due to a transient recovery of ovarian function. It would be desirable to provide all patients, at the end of cancer therapy, with a precise long-term follow-up schedule in accordance with current guidelines (e.g., COG guidelines[1]). Providing treatment summaries and targeted, timely education to patients and families is critical to promoting patient and family engagement,

improving adherence to follow-up, ensuring continuity of care during transitions, enabling early monitoring of complications, and reducing variability in follow-up between centers.

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9.2. Central endocrine complications among childhood cancer survivors treated with radiation therapy: a pentec comprehensive review

Wheeler G, Grassberger C, Samers J, Dwyer M, Wiltshire K, Daly P, Alvarez B, Campbell BA, Kerr AJ, Kron T, Duane FK, Zacharin M, Downie P, Kyriakou E, Ronckers CM, Constine LS, Hiniker SM

Int J Radiat Oncol Biol Phys. 2024 Jun 1;119(2):457-466.

PMID: 37269265. doi: 10.1016/j.ijrobp.2023.04.024.

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Brief summary: This review was conducted within the Pediatric Normal Tissue Effects in the Clinic (PENTEC) project to clarify the risk and incidence of central endocrine toxicity and the resulting pituitary hormone deficiencies in patients undergoing radiotherapy (RT).

Data from 16 papers (19 separate cohorts, totaling 570 patients) reporting toxicity scoring and individual dose levels, or their estimation, were included, with median follow-up ranging from 3.9 to 17.8 years. Since the risk of injury was related to age at RT in previous studies, a subgroup analysis was conducted on cohorts where the patients' median age was over 5 years. The rate of endocrine toxicity increased during the initial few years post-RT, and stabilized at 3 to 5 years, even if this information was reported only by few studies.

The normal tissue complication probability (NTCP) model estimated a 20% risk of GHD in patients with median age >5 years who received 21-Gy in 2-Gy fraction to the HPA. The risk of central hypothyroidism was 20% in children receiving 22-Gy in 2-Gy fraction, while the 20% risk of ACTH deficiency was related to a dose of 34-Gy in 2-Gy fraction; in both these two deficits, the results were just minimally influenced by patient's age.

Comment: In many cases, RT plays a crucial role in treating pediatric cancers located near or involving the hypothalamic-pituitary axis (HPA). Due to the necessity of effectively targeting the tumor, radiation doses to these areas cannot be reduced. This comprehensive review offers valuable insights into the risk of toxicity at specific RT doses to the HPA and should be taken into account during treatment planning. However, it is essential to carefully balance adequate tumor coverage with minimizing radiation exposure to critical organs. This balance must be considered on a case-by-case basis and clearly communicated when advising patients and their families. The primary limitations of this review arise from the heterogeneity of data reported in the included studies. This heterogeneity pertains to: inconsistencies in the definitions of hormone deficiencies, the lack of quantitative hormone measurements or detailed information regarding the severity of deficiencies, reliance on estimated radiation therapy (RT) doses, frequently based on whole-brain irradiation rather than specifically targeting the hypothalamic-pituitary axis, variability in tumor grading at diagnosis, which in some cases necessitated higher RT doses, concomitant therapies such as hormone replacement or chemotherapy, and the baseline endocrine status of patients prior to cancer diagnosis.

9.3. Adult growth hormone deficiency, replacement therapy, and outcomes in long-term childhood cancer survivors

Yoshida T, Baedke JL, Wang H, Chen Y, Yu C, Wilson CL, Mulrooney DA, Dixon SB, Huang IC, Brinkman TM, Krull KR, Mostoufi-Moab S, Martínez JM, Ness KK, Hudson MM, Yasui Y, Delaney A

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Brief summary: This cross-sectional analysis of patients enrolled in the St. Jude Lifetime Cohort Study (SJLIFE) investigated the prevalence of severe adult growth hormone deficiency (aGHD) and its treatment, explored

potential associations with socioeconomic factors, and examined the impact of aGHD on physical, psychosocial, and neurocognitive outcomes.

Detailed information regarding growth hormone deficiency (GHD) diagnosis, as well as the dose and/or duration of growth hormone therapy (GHT), was not available. Therefore, the authors used IGF-1 z-scores as a surrogate marker of GHD/GHT status in cases where a confirmed diagnosis of GHD or documentation of GHT was lacking. Based on this approach, severe aGHD was identified in 354 of 3,902 patients. However, only 9% (32 patients) reported receiving GHT, 286 had mild untreated aGHD, and 3,262 did not have aGHD. Patients in the aGHD group who received GHT had higher socioeconomic status and were more likely to have health insurance compared to the other three groups. This finding was also confirmed in analyses restricted to the aGHD group, showing differences between treated and untreated patients. Low IGF-1 levels, used as a surrogate marker for untreated severe adult growth hormone deficiency (aGHD), were associated with a higher prevalence of abnormal body composition, reduced handgrip strength, adverse metabolic and cardiovascular outcomes, increased neurocognitive disorders, diminished health-related quality of life (QOL), and a higher incidence of depression.

Comment: Among the endocrine consequences in childhood cancer survivors (CCSs), growth hormone deficiency (GHD) is one of the most common, particularly when the hypothalamic–pituitary region is directly affected by the tumor itself and/or its treatment (e.g., radiotherapy). GHD may begin in childhood and persist into adulthood, and if left untreated, is associated with a higher risk of complications compared to adult-onset GHD. This study highlights that untreated adult growth hormone deficiency (aGHD) among adult survivors of childhood cancer is common and associated with a wide range of adverse outcomes. There are several possible reasons for the relatively high number of untreated GHD cases. These include missed diagnoses during routine follow-up, limited awareness regarding indications, benefits, and safety of treatment, and socioeconomic barriers, especially in countries where GH therapy (GHT) is costly and requires health insurance coverage. The value of this large cohort study lies in its focus on the risk of complications in untreated aGHD patients among CCSs, whose survival and QOL are impacted by multiple health issues and may be further compromised by the absence of GHT when needed.

It is essential to implement strategies that ensure appropriate GHT for eligible patients. These include timely diagnosis, even in cases where the tumor did not directly affect the hypothalamic–pituitary axis, clear communication about the importance of GHT for overall health, reassurance regarding potential side effects, socioeconomic support when needed, and, last but not least, a collaborative approach among all specialists involved in the care of CCSs.

Fertility Issues

9.4. Testicular dysfunction in male childhood cancer survivors treated with radiation therapy: a PENTEC comprehensive review

Baliga S, Patel S, Naqa IE, Li XA, Cohen LE, Howell RM, Hoppe BS, Constine LS, Palmer JD, Hamstra D, Olch AJ
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PMID: 37791936. doi: 10.1016/j.ijrobp.2023.08.010.
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Brief summary: This systematic review, by the PENTEC initiative, addresses a critical but often underexamined long-term effect of childhood cancer therapy: testicular dysfunction in male survivors treated with RT.

Following PRISMA guidelines, the authors searched PubMed, Embase, and Web of Science for studies reporting on testicular function after radiation therapy (RT) in male childhood cancer survivors. A total of 1,496 articles were initially identified, 31 studies were analysed, and only 4 studies showed data on testicular dose to generate descriptive scatter plots. Two cohorts were identified: cohort 1 consisted of pediatric and young adult patients with cancer who received scattered (incidental) testis exposure during pelvic RT; cohort 2 consisted of pediatric and young adult patients with cancer who received direct testicular radiation therapy as part of their cancer therapy. The use of chemotherapy, especially alkylating agents and anthracyclines was also analysed.

The risk of oligospermia varied from 44% to 80% when the mean testicular dose was <1 Gy, but this recovered by >12 months in 75% to 100% of patients. At doses >1 Gy, the rate of oligospermia increased to $>90\%$ at 12 months. Testosterone levels were generally unaffected at mean testicular doses <0.2 Gy but were abnormal in up to 25% of patients receiving doses between 0.2 and 12 Gy. Doses between 12 and 19 Gy led to low testosterone levels in 40% of patients, while doses above 20 Gy were associated with low testosterone levels in at least 68% of patients. FSH levels were unaffected by a mean testicular dose <0.2 Gy, whereas at doses above 0.5 Gy, the risk was between 40% and 100%. LH levels were affected at doses above 0.5 Gy in 33% to 75% of patients between 10 and 24 months after radiation. Despite differences in patient populations and treatment regimens, the authors generated a preliminary dose–risk curve, indicating that the risk of testicular dysfunction increases sharply with higher radiation doses.

Comment: This comprehensive review evaluates the dose–response relationship between testicular exposure to radiotherapy (RT) and subsequent impairment of testicular function. Only 4 studies met the criteria for dose–response modelling, highlighting the scarcity of high-quality, detailed data in this area. Even low doses (<2 Gy) can impair spermatogenesis, while higher doses (>20 Gy) are associated with Leydig cell damage, leading to testosterone deficiency. Damage to the testes is often long-lasting or irreversible, especially when high-dose RT is used. Recovery of function is rare once damage has occurred, particularly for testosterone production. Anthracyclines, when combined with RT, may have an additive effect on testicular damage. These findings underscore the importance of minimizing testicular dose during radiotherapy planning in boys, especially when long-term survivorship is expected. Modern and less damaging RT techniques as proton therapy, intensity-modulated radiation therapy (IMRT), and testicular shielding should be strongly considered when feasible.

Parents and patients should be counselled about the potential long-term effects on fertility and endocrine health, including options for fertility preservation. Lifelong monitoring for hypogonadism and infertility is warranted in patients who received significant gonadal irradiation.

9.5. Longitudinal trends in testicular volume z scores from puberty to adulthood, sperm quality, and paternity outcomes after childhood cancer

Korhonen M, Jahnukainen K, Koskela M
Cancer. 2025 Jan 1;131(1):e35623.
PMID: 39470456. doi: 10.1002/cncr.35623.
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Brief summary: This retrospective study evaluated the long-term effects of prior cancer treatments, such as chemotherapy and radiotherapy, on testicular volume, sperm quality and paternity outcomes in 255 male childhood cancer survivors (CCS) who were treated at Helsinki Children's Hospital between 1964 and 2000, from adolescence to adulthood.

Testicular volume was monitored from puberty into adulthood, and semen analyses with hormonal measurements (FSH, LH, inhibin B and testosterone) were performed after age 20. Treatment exposures, including cumulative alkylating agent dose (cyclophosphamide equivalent dose, CED) and testicular radiation, were documented. Outcomes such as testicular volume (Z score), sperm quality, and paternity were then compared between treatment subgroups (such as chemotherapy only vs. chemotherapy plus radiotherapy).

Patients treated with chemotherapy alone showed a delayed but eventual return of their testis volume to normal levels, while those exposed to testicular radiation ≥ 1 Gy had persistently reduced volumes. Increased risk of azoospermia and lower paternity rates was observed with high-dose alkylating agents (CED ≥ 12 g/m^2) and testicular radiation. A testicular volume z-score <-2 strongly predicted azoospermia, and hormonal markers (elevated FSH, low inhibin B) further supported gonadal dysfunction. Improvements in semen parameters over time were most evident in the chemotherapy-only groups.

Comment: This study investigated the different impacts of chemotherapy and radiotherapy on male fertility. The results highlight that testicular volume measurements and serum hormone levels, such as FSH and inhibin B,

can predict the risk of azoospermia. These findings underscore the importance of long-term monitoring and fertility counseling in male CCS exposed to gonadotoxic treatments.

9.6. Interindividual variation in ovarian reserve after gonadotoxic treatment in female childhood cancer survivors - a genome-wide association study: results from PanCareLIFE

van der Perk MEM, Broer L, Yasui Y, Laven JSE, Robison LL, Tissing WJE, Versluys B, et al, PanCareLIFE consortium.
FertilSteril. 2024 Sep;122(3):514-524.
PMID: 38729340. doi: 10.1016/j.fertnstert.2024.05.002.
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Brief summary: This genome-wide association study (GWAS) identified genetic polymorphisms related to increased risk of gonadotoxicity in cancer survivors (CSs), in data from 2 independent CSs cohorts.

The analysis was conducted in 743 patients of the pan-European PanCareLIFE cohort and in 391 of US-based St. Jude Lifetime Cohort (SJLIFE). Since the aim was to identify genetic variants that may explain treatment-related interindividual variability, childhood cancer survivors whose gonadal function was unlikely to be further influenced by genetic variability were excluded. This group included survivors who had received bilateral ovarian irradiation (defined as bilateral irradiation of the abdomen below the pelvic/iliac crest), central nervous system or total body irradiation, as well as those who underwent bilateral oophorectomy or hematopoietic stem cell transplantation.

Three genome-wide significant and 16 genome-wide suggestive loci were associated with anti-Müllerian hormone (AMH) levels, adjusted for cyclophosphamide equivalent dose, age at diagnosis, and age at the study. On the basis of the effect allele frequency and biologic relevance, 15 single nucleotide polymorphisms (SNP) were selected for replication. None of the single SNPs were statistically significantly associated with AMH levels. To identify potential clinical significance of the variants detected, the authors performed a meta-analysis of the results and found that one SNP located on chromosome 1 (rs78861946) showed a borderline genome-wide significance. This revealed a potential association with gonadal damage, expressed as reduction of AMH levels, in CSs treated with high dose of alkylating agents. It is noteworthy that this variant is located in the intronic region of the *RGS5* gene, close to *RSG4* and *NUF2* genes, involved in FSH receptor signalling, cell cycle regulation, follicular atresia and apoptosis, which are underlying mechanisms of natural menopause.

Comment: The increased survival rates after cancer have led to greater attention to gonadotoxic effects and impaired fertility, clarifying specific risk factors such as the use of alkylating agents and/or ovarian radiotherapy, as well as predictors like AMH. Given that age at menopause is influenced by genetic factors in the general population, some studies have been conducted in CSs to identify a genetic basis for the observed variability in premature menopause or likelihood of pregnancy in CSs. This study represents the first application of GWAS to identify polymorphisms associated with reduced ovarian reserve in CSs, involving the comparison of two independent cohorts to assess the reproducibility of the findings. GWAS could represent a valuable tool to find genetic markers to early identify patients needing a closer follow up and accurate support for an increased risk of ovarian damage.

Metabolic Health after Childhood Cancer

9.7. Prevalence and determinants of dyslipidemia in 2338 Dutch childhood cancer survivors: a DCCSS-LATER 2 study

Bolier M, Pluimakers VG, de Winter DTC, Fiocco M, van den Berg SAA, Bresters D, van Dulmen-den Broeder E, van der Heiden-van der Loo M, Höfer I, Janssens GO, Kremer LCM, Loonen JJ, Louwerens M, van der Pal HJ, Pluijm SMF, Tissing WJE, van Santen HM, de Vries ACH, van der Lely AJ, van den Heuvel-Eibrink MM, Neggers SJCMM

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PMID: 39564675. doi: 10.1093/ejendo/lvae149.
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Brief summary: This cross-sectional analysis from the nationwide Dutch Childhood Cancer Survivor LATER 2 Study (DCCSS-LATER2) assessed dyslipidemia among 2,338 adult survivors of childhood cancer (51% male; median age 34.7 years; median follow-up 27.1years). Normative data from 132,226 adults without cancer history from the Lifelines cohort were used as a reference. Logistic regression compared the odds of dyslipidemia between groups (adjusted for age, sex and BMI). Multivariable models identified determinants of dyslipidemia, such as treatment exposures and lifestyle factors.

Childhood cancer survivors had higher odds of dyslipidemia than the reference population, 20.6% had elevated triglycerides (>1.7 mmol/l), 30.3% had low HDL-cholesterol (<1.0 mmol/l in males; <1.3 mmol/l in females), 29.9% had with high total cholesterol (>5.2 mmol/l), 7.3% had high LDL-cholesterol (>4.1 mmol/l), and 7.7% had elevated apolipoprotein-B (>130 mg/dl).

Independent predictors of dyslipidemia included: male sex, older age, higher BMI, smoking, and low physical activity. Treatment-related determinants were abdominal/pelvic RT, cranial RT, total body irradiation, alkylating chemotherapy and secondary endocrine disorders (growth hormone deficiency, diabetes mellitus).

Comment: This study confirms that childhood cancer survivors have an increased risk of dyslipidemia, with nearly one-third having abnormal HDL or cholesterol levels. The analysis, based on a large and representative cohort with long-term follow-up, enhances the generalizability of the findings. The increased risk is driven by both treatment-related exposures and lifestyle factors, highlighting the need for survivor-focused cardiovascular screening and preventive care. This underscores the importance of structured follow-up and early intervention to reduce long-term morbidity and mortality in this vulnerable population. Longitudinal studies are needed to understand the evolution of lipid profiles over time and to evaluate the effectiveness of risk-reduction strategies.

Bone Health after Childhood Cancer

9.8. Attributable risk and consequences of bone mineral density deficits in childhood cancer survivors

Goodenough CG, Baedke JL, Delaney AM, Wilson CL, Brinkman TM, Im C, Ware ME, Inaba H, Clark KL, Armstrong GT, Mulrooney DA, Pui CH, Green DM, Merchant TE, Srivastava DK, Yasui Y, Hudson MM, Robison LL, Kaste SC, Ness KK, Chemaitilly W
JAMA Netw Open. 2025 Jan 2;8(1):e2454069. PMID: 39792384.
doi: 10.1001/jamanetworkopen.2024.54069. Kiri.Ness@StJude.org

Brief summary: This study analysed cross-sectional and longitudinal data from a cohort of 3,919 adult survivors of childhood cancer (median age 32, 53% males) to determine the risk of moderate (≤ 1 SD) and severe (≤ 2 SD) bone mineral density (BMD) impairment, evaluated by lumbar quantitative computed tomography (QCT).

The prevalence of moderate or severe BMD deficits was 22% and 7%, respectively, and was higher in males ($P<0.001$). Severe deficits were associated with young age 5–9 years at cancer diagnosis, high dose of cranial radiotherapy ≥ 30 Gy, testicular or pelvic radiation, underweight, sedentary lifestyle, and smoking. BMD impairment was also associated with hypogonadism and growth hormone deficiency (GHD), which were untreated in 56% and 95% of patients, respectively. Survivors with moderate or severe BMD deficits were less likely to live independently and more likely to require personal assistance, report depressive symptoms, and experience poor quality of life.

Comment: This large study confirms previous findings and reinforces current recommendations that support long-term bone mineral density surveillance for survivors treated with cranial or craniospinal radiotherapy and total body irradiation[1]. Modifiable risk factors (such as hypogonadism, growth hormone deficiency, smoking, and sedentary behaviour) represent important targets for intervention. In particular, the prevalence of untreated hormonal deficiencies should be carefully addressed, especially given the challenges these patients often face in

maintaining regular physical activity. Limitations of the study include: (1) the exclusion of some eligible patients; (2) the absence of data on fractures and spinal X-rays; and (3) the lack of information on factors negatively impacting BMD, such as history of trauma, prevalent scoliosis, prolonged immobilization, or previous traumatic fractures. Finally, the high radiation exposure due to QCT should be avoided, particularly in this patient population. Indeed, even the most recent guidelines clearly recommend DXA as the preferred screening method[1-2].

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Secondary Thyroid Cancer

9.9. Subsequent thyroid carcinomas in children and adolescents registered in the German MET consortium (1997–2023)

Kunstreich M, Ronckers CM, Lorenz K, Wolf SH, Lessel L, Rohrer TR, Vokuhl C, Schmid KW, Luster M, Frühwald MC, Vorwerk P, Redlich A, Kuhlen M

Thyroid. 2025 Jan;35(1):18-30. PMID: 39699646.

doi: 10.1089/thy.2024.0312. Michaela.Kuhlen@uk-augsburg.de

Brief summary: This retrospective multicenter cohort study compared clinical characteristics and outcomes of subsequent differentiated thyroid carcinoma (DTC) in childhood cancer survivors with first primary DTC. It also compared cases of subsequent DTC in patients treated with chemotherapy alone to those treated with both chemotherapy and radiotherapy.

The study analyzed 505 cases of childhood DTC reported to the German Malignant Endocrine Tumour (MET) registry (1997–2023), of which 66 (13.1%) were subsequent DTCs arising after childhood cancer or hematopoietic stem-cell transplant (HSCT). These subsequent DTCs presented at median age 12.7 years, following a median latency period 7.3 years. Compared to primary DTCs, subsequent DTCs were less frequent in females, were smaller (median 1.1 cm vs. 2.2 cm), yet more often multifocal, and were usually detected through surveillance rather than symptoms; however, stage distribution and long-term outcomes did not differ. Among subsequent DTC cases, tumours arising after chemotherapy alone appeared earlier (median age 11.5 years), with a shorter latency (6.2 years) and were of a larger size (1.86 cm) than those following chemo + radiotherapy.

These findings support chemotherapy as an independent risk factor for treatment-related paediatric DTC, likely through DNA damage, genomic instability and treatment-induced mutations or chromosomal aberrations.

Comment: This series represents the largest published cohort of subsequent DTC in children aged 5–18-year-old. It addresses a key knowledge gap left by studies that focused on older adolescents and young adults. Even if DTC is typically associated with radiation exposure, this study shows that survivors treated with chemotherapy alone are also at risk of developing larger thyroid tumors at younger ages and after shorter latency periods. This highlights chemotherapy as an independent risk factor for subsequent DTC. Follow-up protocols should be changed to include customized, ultrasound-based care based on the patient's treatment history and individual risk.

9.10. Thyroid cancer in childhood cancer survivors: demographic, clinical, germline genetic characteristics, treatment, and outcome

Yildirim UM, Kebudi R, İribaşÇelik A, Zülfikar B, Kebudi A

J Clin Med. 2025 Jan 17;14(2):589. PMID: 39860595.

doi: 10.3390/jcm14020589. rejinkebudi@yahoo.com

Brief summary: This single-center retrospective review aimed to characterize thyroid cancer as a second or third malignant neoplasm (SMN) in childhood cancer survivors (CCSs) diagnosed between 1990 and 2018, as well as to identify potential risk factors that could inform tailored follow-up strategies.

Ten of 3,204 CCSs developed thyroid cancer between 4 and 19 years (median: 9 years) after the initial cancer diagnosis. All cases were histologically confirmed as papillary thyroid carcinoma. All patients were diagnosed through thyroid ultrasound and underwent total thyroidectomy, and 3 received radioactive iodine (RAI). No recurrences or deaths related to PTC occurred, with a median follow-up of 5.5 years after diagnosis. All patients had received chemotherapy, and 8 had also been treated with radiotherapy (RT). Genetic screening was performed in 6 of the 10 patients and revealed pathogenic variants in *CHEK2*, *APC*, and *DICER1* genes in 3 individuals, possibly contributing to the increased risk; the remaining tests were negative.

Comment: The onset of second malignant neoplasms (SMNs) is a well-known long-term complication of childhood cancer and represents a leading cause of treatment-related mortality. Thyroid cancer accounts for up to 10% of SMNs and is one of the most common and clinically significant malignancies in CCSs. RT, chemotherapy with alkylating agents or anthracyclines, and targeted therapy with I-131 MIBG (metaiodobenzylguanidine) have all been described as risk factors for thyroid neoplasms. For RT in particular, a dose-dependent relationship has been demonstrated, with the highest relative risk observed at around 20Gy. Beyond this dose, the risk appears to decrease, likely due to radiation-induced thyroid cell death. Alongside these treatment-related factors, genetic predisposition is increasingly recognized as a contributing factor. Compared to previous studies, STC in this cohort appeared to occur earlier during follow-up, particularly in patients who had received RT. Alkylating agents and anthracyclines were identified as additional independent risk factors for STC. Therefore, all treatments, including I-131 MIBG, must be considered when assessing long-term risk in CCSs.

The risk of developing a second thyroid cancer necessitates careful long-term follow-up, to be initiated no later than 5 years after RT, as recommended by the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. In this study, genetic testing revealed mutations in the Cell Cycle Checkpoint Kinase 2 (*CHEK2*) and Adenomatous Polyposis Coli (*APC*) genes, which may contribute to increased cancer risk. The authors emphasized the importance of genetic screening, which could help guide personalized follow-up strategies. The *CHEK2* gene encodes a protein kinase involved in the DNA damage response, cell cycle checkpoint regulation, and maintenance of genomic stability. Mutations in *CHEK2* compromise these critical cellular functions, leading to increased susceptibility to malignancies. Individuals with familial adenomatous polyposis, caused by pathogenic germline mutations in the *APC* gene, are at significantly increased risk of developing papillary thyroid cancer in addition to colorectal polyps.

Endocrine Health in Chronic Non-Neoplastic Diseases

9.11. Growth and recombinant human growth hormone use in children with congenital chronic kidney disease: a multicentric contemporary study

Dubois S, Duneton C, Salomon R, Ulinski T, Boizeau P, Carel JC, Simon D
Horm Res Paediatr. 2025 Jan 16:1-9.
PMID: 39820089. doi: 10.1159/000543435. jean-claude.carel@aphp.fr

Brief summary: This multicenter cohort study in France evaluated recombinant human growth hormone (rhGH) treatment patterns and growth outcomes in 87 patients with congenital chronic kidney disease (CKD) who underwent kidney transplantation between the ages 3 to 18 years. Of these, 48% received GH therapy, prescribed either by nephrologists (52%) or endocrinologists (48%).

The median age at GH treatment initiation was 7.4 years (range: 3.4–10.7), at median height –2 SDS. The starting rhGH dose was 0.044 mg/kg/day, and the median dose at follow-up was 0.036 mg/kg/day. Two-thirds of the prescriptions deviated from the French authorization criteria, which include the following: height $\leq$ –2 SDS

or growth velocity < 2 cm/year, age > 2 years, GFR < 60 mL/min/1.73 m^2, bone age < 11 years in girls and < 13 years in boys, at least 1 year of nephrological management, and absence of active malignancy. Endocrinologists typically prescribed rhGH for patients under 2 years of age, whereas nephrologists did so for those with height above –2 SDS. The median height gain was +0.7 SDS over 1.7 years. Growth response was negatively associated with older age at GH initiation and being on dialysis at treatment start. 52% of patients did not receive rhGH treatment. From CKD diagnosis to kidney transplantation, untreated patients experienced a median height loss of −0.6 SDS, and half of them had height SDS < −2 at transplantation. Reasons for not receiving rhGH therapy included spontaneous catch-up growth, active malignancy or near-final height.

Comment: This is the first French multicenter cohort study since the approval of rhGH treatment for CKD in 1995. It raises important questions about the criteria for rhGH prescription in these patients, which are still not universally defined[1,2]. For example, the European consensus recommends starting GH therapy in patients with height between the 3rd and 10th percentile and growth velocity <25th percentile[2]. This study also highlights the need to clarify the optimal methods for monitoring therapy. The authors note that the mean height gain in SDS was lower than that reported in the literature, likely attributable at least in part to GH dosing. Indeed, although treatment was initiated at appropriate doses, follow-up adjustments were often not made in response to either weight gain or IGF-1 levels. Moreover, conclusions regarding untreated patients are limited by the lack of data on target height, pubertal stage, and bone age. Study limitations include missing information on pubertal status and target height for a significant proportion of patients, a relatively small cohort size, and a short follow-up duration. Further studies with larger sample sizes and prolonged follow-up extending through final height attainment are warranted. As the authors rightly emphasize, improved collaboration between nephrologists and endocrinologists is essential to optimize the initiation and monitoring of rhGH therapy in children with CKD.

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9.12. Ovarian histology in children with classic galactosemia and correlation with endocrine and metabolic markers

Badger T, Kastury R, Kavarthapu R, Balasubramanian R, De La Luz Sierra M, Lou H, Abbott C, Yano JC, Gomez-Lobo V.
FertilSteril. 2024 Oct;122(4):744-746.
PMID: 38761847. doi: 10.1016/j.fertnstert.2024.05.146.
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Brief summary: This cross-sectional study investigated ovarian histology in young girls with classic galactosemia (CG) and linked these findings with hormonal and metabolic indicators of premature ovarian insufficiency.

Eight prepubertal girls with a confirmed diagnosis of CG undergoing ovarian tissue cryopreservation (OTC) via laparoscopic unilateral oophorectomy were included. Eight prepubertal girls without CG who were undergoing OTC before receiving gonadotoxic therapy for different diagnoses were included as controls. Ovarian biopsies were taken and examined for follicle count (primordial, primary, secondary), evidence of fibrous "streak" stroma or normal ovarian architecture. Hormonal and metabolic biomarkers (anti-Müllerian Hormone (AMH), FSH, LH, oestradiol and galactose-1-phosphate (gal-1-p) were measured.

Younger girls (age <5years) often had normal follicle counts, while older prepubertal girls more commonly showed absent or reduced follicles, sometimes replaced by fibrotic stroma. Most patients had low AMH, indicating early decline in ovarian reserve. Elevated FSH levels were observed while FSH bioactivity remained within normal range, supporting the hypothesis of direct ovarian damage rather than abnormal hormonal signalling. Patients with no detectable follicles also had nearly undetectable AMH and high FSH levels, supporting the association between histological damage and endocrine insufficiency. Younger age at the time of the biopsy corresponded to more intact ovarian histology and relatively preserved AMH. There was a strong negative correlation between gal-1-p values at 0–1 month and 1–6 months of life, and mean follicular density at the time of OTC.

Comment: This evidence enhances our understanding of the impact of classic galactosemia on the ovaries by linking histological findings with biochemical markers. The cross-sectional design and small sample size limit inference on the precise timeline of follicular depletion, but the findings support early fertility counselling and consideration of fertility preservation techniques (e.g., ovarian tissue cryopreservation) in childhood, where ethically and medically feasible. A longitudinal study starting in infancy with early and serial AMH monitoring and non-invasive ovarian imaging could clarify the progression rate of ovarian damage and help identify at-risk girls before significant follicular loss. Molecular analysis of ovarian cells (e.g., single-nucleus transcriptomics) may elucidate the pathophysiology of ovarian damage, such as endoplasmic reticulum (ER) stress or DNA damage pathways.

9.13. Endocrine manifestations and long-term outcomes of patients with mitochondrial diseases

Kim JH, Kim D, Hwang S, Kim GH, Lee BH, Yoo HW, Choi JH.
Orphanet J Rare Dis. 2025 May 17;20(1):235.
PMID: 40382647. doi: 10.1186/s13023-025-03773-6. jhc@amc.seoul.kr

Brief summary: This single centre, retrospective study evaluated endocrine manifestations in 54 patients with primary mitochondrial diseases (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, MELAS; Pearson syndrome; Kearns–Sayre syndrome, KSS) at mean age 18.5 years (range 0.1–43).

Approximately half of MELAS patients had short stature, which was already present at diagnosis in half of these cases, as well as low body weight. 29 of 43 patients had short final height. Similarly, about half of the patients had previously diagnosed diabetes mellitus (mean age at diagnosis: 26 years, range 12–50; mean HbA1c: 7.9%, mean glucose level: 385 mg/dl). 10 of 23 patients presented with diabetes prior to MELAS diagnosis, with a median interval 10 years from diabetes onset. 5 of 49 patients were diagnosed with papillary thyroid carcinoma, at mean age at diagnosis 34 years.

Comment: This Korean study shows that patients with primary mitochondrial disease may manifest a wide spectrum of endocrine dysfunctions, often accompanied by multiorgan and particularly neurological abnormalities. Endocrinologists should consider mitochondrial diseases in patients presenting with short stature, low BMI, diabetes mellitus, and neurological features such as developmental delay or hearing loss. The presentation of diabetes mellitus can precede the diagnosis of mitochondrial disease, is usually indolent, and should not be treated with metformin due to the risk of precipitating lactic acidosis. The suspected association between papillary thyroid cancer and MELAS appears significant and requires confirmation in larger case series. Study limitations include the retrospective design, which resulted in missing data and a limited sample size. Furthermore, growth assessment was incomplete due to the lack of essential data such as target height, pubertal status, bone age, and GH response to stimulation tests.

10. Type 1 Diabetes

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Clinical Trials

10.1. Fully closed-loop improves glycemic control compared with pump with CGM in adolescents with type 1 diabetes and HbA1c above target: a two-center, randomized crossover study

Kadiyala N, Lakshman R, Allen J, Ware J, Boughton CK, Wilinska ME, et al

Diabetes TechnolTher. 2025. May 30. Online ahead of print.

PMID: 40445776 doi: 10.1089/dia.2025.0062.

Brief summary: This two-center, randomized, crossover study assigned 24 adolescents (13-19 years) with type 1 diabetes (T1D) on insulin pump therapy and with above-target HbA1c to two 8-week periods of unrestricted living, comparing a fully closed loop (FCL) insulin delivery system to standard nonautomated insulin pump therapy with continuous glucose monitoring (CGM). The FCL system improved glucose outcomes and was safe.

Closed-loop systems have substantially changed the management of T1D in children and adolescents (1). However, these systems are primarily hybrid, requiring users' input in certain situations, particularly at mealtimes. FCL systems, which eliminates the need for carbohydrate counting and pre-meal bolusing, have so far only been explored in a few clinical studies in adults with T1D or Type 2 diabetes (2,3). No data are available for adolescents with T1D, a population that struggles more than other age groups to achieve recommended HbA1c targets, even when using a closed-loop system (4). This is often due to missed or insufficient mealtime insulin doses (5).

This trial reports on the safety and efficacy of a FCL insulin delivery (CamAPS HX) in 24 adolescents with T1D and suboptimal glycemic outcomes, as indicated by a median HbA1c of 74 mmol/mol [8.9%], under unrestricted living conditions, using a cross-over design. FCL use was safe and led to a better percentage of time with glucose in target range (TIR) (primary endpoint 3.9-10.0 mmol/l) compared to nonautomated pump (45.2% vs. 32.3%), and lower time spent in hyperglycemia (time above range, TAR) ($>$13.9 mmol/l) (28.7% vs. 39.6%). The achieved TIR in the FCL group was below the recommended target ($>$70%), but was much better than the baseline value (37%). No differences were found in the percentage of time spent in the hypoglycemia range (glucose $<$3.9 mmol/l), Hb1Ac and total daily insulin dose.

Although the study was limited by a small sample size, short duration (8 weeks), and recruitment from only two UK clinical sites, the findings are nonetheless encouraging. FCL systems may offer a novel approach to improveglycemic outcomes and reduce diabetes-related distress in the vulnerable adolescent population with T1D.

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10.2. Ustekinumab for type 1 diabetes in adolescents: a multicenter, double-blind, randomized phase 2 trial

Tatovic D, Marwaha A, Taylor P, Hanna SJ, Carter K, Cheung WY, et al
Nat Med. 2024;30(9):2657-66.
PMID: 39079992

Brief summary: In this phase 2, multicentre double-blind, randomized, placebo-controlled trial, the monoclonal antibody Ustekinumab was compared to placebo in 72 adolescents (aged 12–18 years) with recent-onset stage 3 type 1 diabetes (T1D). After 12 months, stimulated C-peptide was 49% higher in the Ustekinumab group compared to placebo. Preservation of C-peptide was associated with a reduction in a subset of T helper 17 cells.

Immunotherapy, aimed at modulating the autoimmune response in T1D, has been shown to delay the loss of β-cell function and remains a focus of intensive clinical and translational research (1).

Ustekinumab is a monoclonal antibody that binds to the shared p40 subunit of interleukin (IL)-12 and IL-23, targeting the development of T helper 1 cells and T helper 17 cells (TH1 and TH17), known to be implicated in the pathogenesis of T1D (2). Ustekinumab (STELARA) has been licensed since 2009 for the treatment of psoriasis, psoriatic arthritis and inflammatory bowel disease, including use in children as young as 12 years for some indications.

In this trial, which was conducted in 16 UK clinical sites, Ustekinumab, administered subcutaneously every 4-8 weeks, for a total of 7 injections, exerted a positive effect on β-cell preservation in adolescents with a recent diagnosis of stage 3 T1D. While there was no difference in the primary outcome (C-peptide area under the curve during a mixed meal tolerance test) at 28 weeks, a significant between-group difference emerged at 56 weeks, when stimulated C-peptide was 49% higher in the Ustekinumab compared to placebo group. Treatment was well tolerated with no increase in adverse events. Exploratory data suggested a role for a subset of T_H17 cells, modulated by Ustekinumab, with benefits on β-cell preservation.

Of note, the delayed effect of Ustekinumab at 52 weeks suggests that this drug might be useful in combination with other treatments, e.g. to prolong the effect of Teplizumab. The safety and effectiveness data from this trial also supports the rationale to use Ustekinumab in a prevention study in presymptomatic T1D as a next step.

Further larger studies are needed to better assess the effectiveness of Ustekinumab on additional key outcomes, such as glycemic outcomes, for which the current study was not sufficiently powered. Expanding the study population to include younger age groups is also necessary.

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10.3. Adjunct-to-insulin therapy using SGLT2 inhibitors in youth with type 1 diabetes: a randomized controlled trial

Mahmud FH, Bjornstad P, Clarson C, Clarke A, Anthony SJ, Curtis J, et al
Nat Med. 2025. Jun 6. Online ahead of print.
PMID: 40481206 doi: 10.1038/s41591-025-03723-6.

Brief summary: In this 22-week, double-blind, randomized, placebo-controlled study, dapagliflozin (5mg) used as an adjunct therapy to insulin was compared to placebo in 98 youth (age 12-21 years) with type 1 diabetes (T1D). Dapagliflozin reduced measured GFR (mGFR) and HbA1c, and improved time in range (TIR) and BMI.

Sodium-glucose cotransporter type 2 inhibitors (SGLT2i), such as dapagliflozin and empagliflozin, are drugs which increase urinary glucose excretion by blocking glucose reabsorption in the renal proximal tubule and improve glucose levels in an insulin-independent manner (1). Extensive evidence suggests cardio-renal benefits in adults with type 2 diabetes (2). In adults with T1D, the use of SGLT2i as an adjunct therapy to insulin was associated with significant reductions in HbA1c and body weight and improved renal function (3).

The ATTEMPT (Adolescent Type 1 Diabetes Treatment with SGLT2i for Hyperglycemia and Hyperfiltration Trial) trial tested the efficacy and safety of dapagliflozin in youth with T1D from North America. Compared to placebo, treatment with dapagliflozin decreased mGFR by 8.8 ml min^{-1} 1.73 m^{-2}, HbA1c by 0.47%, and increased TIR (glucose levels 4-10 mmol/l) by 9.0%. Dapagliflozin also resulted in a 1.2 kg/m^2 BMI reduction. Notably, when combined with ketone monitoring and a DKA risk mitigation strategy, there were no differences in the rates of ketosis, DKA, genitourinary tract infections, or hypoglycemia between the dapagliflozin and placebo groups.

Improvement in renal function, along with reductions in BMI and improved glycemia, may lead to positive outcomes, particularly in overweight and obese youth, during the challenging adolescent and young adult period characterized by persistently high HbA1c and suboptimal TIR (4).

Limitations of this study include the short treatment period (16-weeks), a relatively low mean HbA1c compared to that reported in North America registries, and the inclusion of participants primarily with normoalbuminuria and a high GFR. Further studies in larger, more diverse cohorts with longer follow up are needed to confirm the reported favorable renal and metabolic effects and the acceptable safety profile of dapagliflozin.

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Important for Clinical Practice

10.4. Data-driven phenotyping of presymptomatic type 1 diabetes using longitudinal autoantibody profiles

Ghalwash M, Anand V, Ng K, Dunne JL, Lou O, Lundgren M, et al

Diabetes Care. 2024;47(8):1424-31.

PMID: 38861550

Brief summary: This study evaluated the risk of progression to stage 3 T1D (clinically manifested) using a novel similarity algorithm and data from 1,845 children (from 5 prospective longitudinal cohorts) at genetic risk for type 1 diabetes (T1D) who developed at least one islet autoantibody (IAb). Persistent positivity for 3 IAbs during a 5-year period emerged as the highest risk for developing diabetes (69.9%), while the lowest risk (1.6%) was with single and transient IAb positivity.

Presymptomatic T1D is characterized by the presence of autoantibodies (IAb) against pancreatic islet beta cell antigens (1). Testing for IAbs enables the identification of individuals in the early-stages of T1D who have a variable risk of progressing to clinical T1D (stage 3), depending on the number and type of Iab, as well as the individual's age. Characterizing IAb patterns over time may aid in stratifying individuals by their risk of progression (2).

In the reported T1DI (Type 1 Diabetes Intelligence) study, genetically susceptible children were divided into 5 clusters based on age at seroconversion (appearance of IAb), order of appearance of at least one of 3 measured IAbs (insulin autoantibody [IAA], GAD antibody [GADA] or islet antigen 2 antibody [IA-2A]) and variation in positivity of IAb types, to determine which cluster carried the highest risk for progression to stage 3 T1D. The highest 5-year risk (69.9%) of progression from first positive IAb to stage 3 T1D was observed in the cluster with all 3 IAbs positivity. Lower risk were found in the cluster with persistent IAA and GADA positivity (39.1%), and with persistent GADA and IA-2A (30.9%). The lowest risk (1.6%) was associated with single and transient IAb positivity, either IAA or GADA.

This study provides important insights into the rates of progression to stage 3 T1D by defining temporal patterns of Iab, and proposing an algorithm applicable even in cohorts with different IAb sampling intervals (every 0.6-2

years). Understanding the various progression pathways can inform the design of targeted clinical trials aimed at preventing T1D. In addition, this information will be valuable for counseling individuals with IAb positivity about their risk of progression.

Strengths of this study include the large sample size (>260,000 samples) and long follow-up (median 12.3 years). However, lack of assessment of the ZnT8 antibody and the exclusion of additional informative variables in the algorithm, such as IAb titer, are potential limitations. Future studies are needed to validate these findings in other cohorts.

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New Biomarkers

10.5. Genetics of circulating proteins in newborn babies at high risk of type 1 diabetes

Tutino M, Yu NY, Hatzikotoulas K, Park YC, Kreitmaier P, Katsoula G, et al

Nat Commun. 2025;16(1):3750.
PMID: 40263317

Brief summary: This study generated a genome-wide protein quantitative trait loci (pQTL) map from 1,985 proteins in 695 newborns at high genetic risk of developing Type 1 diabetes (T1D). A total of 535 pQTLs were identified, of which 62 were characteristic of newborns. Colocalization analysis revealed 5 pQTLs that overlapped with T1D GWAS signals. Mendelian randomization provided causal evidence implicating each of these 5 proteins in T1D aetiology.

Progress in genomics and proteomics holds promise for further uncovering disease mechanisms and guiding the development of preventive therapies in T1D (1). This study explored whether combining genetic data with circulating blood proteomics at birth can identify stable and infancy-specific pQTLs, which could be used as early-life biomarkers and provide mechanistic insights into T1D.

Circulating protein levels were measured by the Olink Explore panel in dried blood spots collected from 695 newborns enrolled in the GPPAD POInT trial (2). These newborns were at genetically increased risk of developing T1D. Imputed genotype data were also available for the same newborns, enabling the integration of genetic and proteomic information.

After quality control, 1,985 proteins were retained for analyses. A GWAS analysis identified 535 pQTL, including 352 cis-pQTLs (variants near the encoding gene) and 183 trans-pQTLs (variants distant from the gene). These findings showed good concordance with pQTLs in adults. Of note, 62 novel, newborn specific pQTLs enriched for the insulin signalling pathway were identified.

Colocalization analyses revealed that pQTLs for 5 proteins aligned with T1D GWAS risk loci: CTRB1, APOBR, IL7R, CPA1, and PNLIPRP1. Importantly, Mendelian randomization analysis suggested that these 5 proteins may each play a causal role in the development of T1D.

Although these findings need to be replicated and validated in larger, more diverse cohorts, they suggest that newborn blood protein profiles may aid in identifying potential drug targets and support the development of early-life diagnostics.

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10.6. A microRNA-based dynamic risk score for type 1 diabetes

Joglekar MV, Wong WKM, Kunte PS, et al

Nat Med 2025. Jun 5. Online ahead of print.
PMID: 40473952 doi: 10.1038/s41591-025-03730-7

Brief summary: This study developed an artificial intelligence–driven, microRNA-based multi-context dynamic risk score (DRS) using 5,983 samples from people with and without type 1 diabetes (T1D) from 7 countries. This DRS was validated for its ability to enable T1D discrimination, correct misdiagnoses, and predict therapeutic responses, thereby establishing a personalized, adaptive framework for T1D risk monitoring and intervention.

Identifying individuals at high risk of T1D and how they progress over time is crucial to guide risk-based monitoring and treatment strategies (1). Current T1D screening relies on autoantibodies and/or genetic risk scores (GRS), but these have limitations. Autoantibodies clearly identify individuals with early stages of T1D but they mark only the initial disease stage and do not provide information on when progression will occur (1). GRS offers static risk prediction, despite T1D risk being influenced over time by environmental and therapeutic factors. Thus, there is a need for a dynamic risk score (DRS).

These researchers developed a DRS for T1D based on circulating microRNAs, which are known to reflect environmental influences. Using data from diverse, multicenter, multiethnic, and multinational ("multicontext") cohorts, they identified 50 microRNAs associated with functional β-cell loss through both experimental and computational analyses. These microRNAs were measured in 2,204 individuals across four distinct contexts (Australia, Denmark, Hong Kong SAR China, and India), resulting in a four-context miRNA-based DRS that effectively distinguished individuals with and without T1D. Generative artificial intelligence was then used to enhance this model, achieving strong predictive accuracy (AUC = 0.84) in an independent validation cohort of 662 participants. The DRS also accurately predicted exogenous insulin requirement within one hour of islet transplantation. Additionally, in a clinical trial of imatinib, the baseline miRNA signature, but not traditional clinical metrics, successfully differentiated responders from non-responders at one year.

This study introduced a microRNA-based DRS capable of distinguishing T1D, correcting misdiagnoses (T1D vs Type 2 diabetes), and predicting therapeutic outcomes. This DRS offers a promising tool for longitudinal risk screening and more precise management of individuals with T1D. There is now a need for its validation and refinement by including additional biomarkers (e.g. T1D antibodies) to improve its predictive performance.

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10.7. Early detection of β-cell decline using home dried-blood-spot c-peptide levels in new-onset type 1 diabetes

Hendriks AEJ, Marcovecchio ML, Evans ML, Barker P, Burling K, Overbergh L, Mathieu C

Diabetes Care. 2025 May 22:dc250214.
PMID: 40402094 Online ahead of print. doi: 10.2337/dc25-0214.

Brief summary: This observational study, in a subgroup of the INNODIA cohort (n = 292, age 1-45 years-old) with a recent diagnosis of stage 3 type 1 diabetes (T1D), assessed the feasibility of measuring dried blood spot (DBS) C-peptide levels, collected at home, as an alternative to the gold standard mixed-meal tolerance test (MMTT) to assess β-cell function during the first 12 months post-diagnosis. Liquid meal stimulated DBS C-peptide levels in the first 6 months post-diagnosis predicted MMTT stimulated C-peptide levels at 12 months.

The need for early detection of β-cell decline in people with newly diagnosed clinical T1D is particularly important in the context of emerging immunotherapy trials. The area under the curve (AUC) of stimulated C-peptide during a 2-h MMTT is the accepted gold standard measure of β-cell function (1). However, MMTT is an invasive and time-consuming procedure that requires attendance at clinical/research settings. Previous clinical trials have shown the need of a minimum follow-up of 12 months to detect an effect of interventions on MMTT C-peptide. Thus, there is a need for biomarkers that can capture differences in β-cell function earlier.

This study assessed an alternative method, monthly DBS C-peptide measurements collected at home, both fasting and 60 min after a liquid meal. Data were collected from 292 people (mean age 12.7 years) with newly diagnosed stage 3 T1D from the INNODIA Natural history study (2). The slopes of post-load DBS C-peptide levels in the first 6 months post-diagnosis predicted MMTT AUC C-peptide and peak C-peptide levels at 12 months. In contrast, the 6-month fasting DBS C-peptide slope did not predict 12-month MMTT AUC C-peptide.

The study results support the feasibility and potential clinical utility of home DBS C-peptide assessment for monitoring β-cell function in individuals with newly diagnosed stage 3 T1D. The ability to collect DBS samples at home enables frequent monitoring without the need for repeated clinic visits. This method has the potential to streamline clinical trials by reducing the follow-up period needed to assess drug efficacy. However, additional validation is required to establish its reliability and wider applicability in both research and clinical settings.

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Hot Topic

10.8. Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient

Wang S, Du Y, Zhang B, et al
Cell 2024; 187(22):6152-6164.e18.
PMID: 39326417

Brief summary: This is a preliminary analysis of a first-in-human phase I clinical trial assessing the feasibility of autologous transplantation of chemically induced pluripotent stem-cell-derived islets (CiPSC islets) beneath the abdominal anterior rectus sheath for T1D treatment. In the first treated patient, this approach resulted in tolerable safety and promising restoration of exogenous-insulin independent glycemic control at 1-year follow-up.

Human induced pluripotent stem cells (iPSCs) show remarkable potential as an unlimited cell source for cellular replacement therapies such as islet transplantation, due to their ability to self-renew and differentiate into functional cell types (1).

In this study, a novel approach was tested, consisting in the use of chemically induced pluripotent stem cells (CiPSCs), generated using small-molecule chemicals as reprogramming factors, for the creation of islet-like cells (CiPSC-islets). Additionally, a new transplantation strategy for CiPSC-islets was implemented, involving an extrahepatic site.

The reported results are from the first treated patient, a 25-year-old woman with 11-year diabetes duration and challenging diabetes management. Patient-derived iPSCs were generated from adipose-derived mesenchymal stromal cells isolated from the patient's adipose tissue using a chemical reprogramming strategy, obtaining patient-specific CiPSCs, which were differentiated into CiPSC-islets. The latter were injected underneath the abdominal anterior rectus sheath of the patient, a location which allowed monitoring though ultrasound and magnetic resonance imaging.

Remarkably, the patient achieved sustained insulin independence starting 75 days post-transplantation. Time-in-target glycemic range increased from baseline 43% to 96% by month 4 post-transplantation, accompanied by a decrease and normalization in HbA1c. Thereafter, the patient showed stable glycemic control, and after 12 months, all study endpoints were met without any safety concerns.

This study reports encouraging clinical outcomes in the first patient, and there is considerable interest in the forthcoming results from the 2 additional patients who have received the same treatment. These findings support continue clinical research in this area and represent meaningful progress toward broader application of the evaluated techniques.

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10.9. Glucose-sensitive insulin with attenuation of hypoglycaemia

Hoeg-Jensen T, Kruse T, Brand CL, et al
Nature 2024;634(8035):944-951.
PMID: 39415004

Brief summary: This study reports the design and properties of NNC2215, an insulin conjugate with a bioactivity reversibly responsive to ambient glucose, due to a switch between an active and less-active conformation status. The insulin receptor affinity for NNC2215 increased 3.2-fold following glucose increases from 3 to 20 mM. In animal models, NNC2215 was able to protect against hypoglycemia while partially covering glucose excursions.

Developing glucose-sensitive insulins that can automatically adjust their activity in response to fluctuations in blood glucose levels has long been a key goal to improve diabetes management (1).

NNC2215 was created by modifying human insulin at specific regions and consists of an insulin backbone (DesB30 Human insulin -degludec), a glucose-binding macrocycle (ring shaped molecule) in the B29 region anda glucoside (glucose-derived molecule) in the B1 region. At high glucose concentrations, glucose binds to the macrocycle leading to an open conformation, whereas at low glucose concentrations, the glucoside occupies the macrocycle, putting NNC2215 into a closed conformation, with a low affinity for the insulin receptor, thus preventing hypoglycemia.

Safety and effectiveness of NNC2215 were tested through various *in vitro* experiments using genetically modified hamster kidney cells and *in vivo* using animal models (mice and pigs).

In insulin receptor-binding studies, NNC2215 demonstrated a 12.5-fold increase in insulin receptor binding affinity when glucose was raised from 0 to 20 mM and a 3.2-fold increase for changes from 3 to 20 mM. In animal studies, NNC2215 demonstrated glucose-responsive behavior by adjusting insulin release according to blood glucose levels in rats. In pig models, it also showed a protective effect against hypoglycemia. NNC2215 could compensate for up to 30% of additional human insulin when lower doses of NNC2215 were administered.

NNC2215 shows potential to enhance diabetes treatment by reducing the risk of hypoglycemia and partially addressing the need for rapid-acting mealtime insulin. This may enable more aggressive insulin titration than is currently possible. However, it remains to be determined whether NNC2215 can accurately respond to fluctuations in glucose levels within a tighter more physiological glycemic range. Clinical trials are also needed to establish the safety and efficacy of NNC2215 in humans.

Reference

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10.10. A bioinspired polymeric membrane-enclosed insulin crystal achieves long-term, self-regulated drug release for type 1 diabetes therapy

Xu J, Zhang Y, Zhao S, Zhang J, Wang Y, Liu W, et al.
Nat Nanotechnol. 2025 May;20(5):697-706.
PMID: 40011600

Brief summary: A nuclear envelope–inspired membrane was developed to coat insulin crystals, enabling long-acting, self-regulated insulin delivery. The resulting i-crystal, featuring electro-responsive porous channels, allowed glucose- and ketone-triggered insulin release. With high drug-loading capacity and zero-order release kinetics, the i-crystal maintained blood glucose control for over one month in mice with type 1 diabetes (T1D).

Numerous efforts have been made to develop "smart insulin" systems that combine long-acting effects with responsiveness to ambient glucose and/or ketone levels. Various strategies have been explored, including glucose-binding polymers, glucose oxidase-based systems, and insulin analogs with glucose-sensitive modifications (1,2).

These investigators designed a nuclear envelope–inspired polymeric nano-membrane that is conformally synthesized around insulin crystals. This membrane integrates glucose- and ketones (β-hydroxybutyrate)-

responsive microdomains and features nanopores that enable sustained, zero-order insulin release. Under hyperglycemia and ketonemia, these microdomains induced a negative membrane potential, triggering the expansion of nanopores and accelerating insulin release.

In preclinical models, this new insulin product demonstrated impressive performance: normoglycemia was maintained for over one month in T1D mice and up to three weeks in diabetic minipigs.

This innovative approach represents a major advancement in drug delivery technology. By combining zero-order release kinetics with metabolite-responsive control, it holds the potential to provide continuous, stable, and predictable insulin delivery. The ability to dynamically respond to fluctuations in glucose and ketone levels enhances its safety and efficacy, reducing the risk of both hypoglycemia and hyperglycemia. This work opens promising avenues for next-generation long-acting therapies for a better management of diabetes.

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New Mechanisms

10.11. Hypoglycemia promotes inner blood-retinal barrier breakdown and retinal vascular leakage in diabetic mice

Guo C, Niu Y, Pan X, Sharma D, Lau E, Jin Y, et al

Sci Transl Med. 2025;17(796):eadq5355.

PMID: 40305573

Brief summary: This experimental study in mouse models showed that even transient episodes of hypoglycemia lead to the accumulation of the transcription factors hypoxia-inducible factor-1α (HIF-1α) and HIF-2α in the retina. This accumulation promotes the expression of vasoactive mediators, resulting in increased retinal permeability and breakdown of the inner blood-retinal barrier (iBRB). Intravitreal administration of a small-molecule HIF-1/2α inhibitor prevented both iBRB disruption and hypoglycemia-induced retinal vascular hyperpermeability.

Diabetic retinopathy (DR), characterized by the breakdown of the inner blood–retinal barrier (iBRB), is a major vascular complication of diabetes and a leading cause of vision loss (1). While hyperglycemia is a key risk factor in the development of DR, evidence also suggests an increased risk during periods of rapid glucose improvement (2). This is a timely concern in the era of automated insulin delivery systems, which often lead to swift glucose correction. Previous research from the authors of the present paper showed that transient hypoglycemic episodes caused the accumulation of HIF1α in retinal glial cells, leading to increased expression of HIF-dependent vasoactive mediators that exacerbated vascular leakage (3).

To further explore these findings, they used mouse models where they show that hypoglycemia resulted in the accumulation of HIF-1α and HIF-2α and the expression of several HIF-dependent vasoactive agents. These factors were not sufficient to induce iBRB breakdown in the retinas of healthy mice but did so in the retina of mice with streptozotocin-induced diabetes.

Genetic deletion of *Hif1a* or *Hif2a* alone was insufficient to prevent the increased expression of vasoactive factors during hypoglycemia. In contrast, in diabetic mice, intravitreal administration of 32-134D, a dual HIF1α and HIF2α inhibitor, prevented the increase in expression of HIF-regulated vasoactive genes after transient episodes of hypoglycemia, blocking both breakdown of the iBRB and the promotion of retinal vascular hyperpermeability.

These findings are relevant because they explain why people with diabetes experiencing rapid improvements in their glycemia may have worsening of their DR and provide the foundation for clinical studies assessing HIF inhibition with 32-134D for its prevention.

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3. Guo C, Deshpande M, Niu Y, *et al*. HIF-1α accumulation in response to transient hypoglycemia may worsen diabetic eye disease. Cell Rep 2023;42(1):111976.

10.12. Neuronal CCL2 responds to hyperglycaemia and contributes to anxiety disorders in the context of diabetes

Pan K, Gao Y, Zong H, et al

Nat Metab 2025;7(5):1052-1072.

PMID: 40329008 doi: 10.1038/s42255-025-01281-2

Brief summary: This experimental study showed that, in a mouse model of streptozotocin-induced diabetes, increased expression of the pro-inflammatory chemokine CCL2 in neurons leads to an increase in anxiety-like behaviours during hyperglycemia. Blocking CCL2 signalling in the brain caused notable reductions in these behaviours, which suggests that this chemokine has a role in anxiety induced by diabetes.

Anxiety disorders are frequently observed in individuals with diabetes and may be linked to various diabetes-related factors (1). This study provides strong evidence that hyperglycemia is a major cause for the development of anxiety disorders through a C-C motif chemokine ligand 2 (CCL2)-dependent mechanism, at least in a mouse model of diabetes.

CCL2 levels were increased in brain samples (medial prefrontal cortex and ventral hippocampus) from streptozotocin-induced diabetic mice and were directly linked to the anxiety-like behaviors in this animal model. The increase in neuronal CCL2 emerged to be related to the activation of the Transcription factor tonicity-responsive enhancer-binding protein (TonEBP) pathway. It was shown that once activated, neuronal CCL2 binds to its receptor CCR2, leading to the activation of microglia and peripheral monocytes, which drive neuroinflammation in the brain.

Intracerebroventricular injection of an anti-CCL2 antibody led to reduced anxiety-like behaviors in the diabetic mice. Clinical transcriptomic analyses of human diabetic brains showed a marked activation of the TonEBP-CCL2-inflammatory pathway, confirming the relevance of these findings in humans.

These findings suggest that CCL2–CCR2 signaling is activated by hyperglycemia and promotes neuroinflammation, thereby exacerbating anxiety. These results offer new insights into the connection between diabetes and mental health disorders. Future research should explore the involvement of additional brain regions in hyperglycemia-induced anxiety.

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10.13. Immune perturbations in human pancreas lymphatic tissues prior to and after type 1 diabetes onset

Golden GJ, Wu VH, Hamilton JT, Amses KR, Shapiro MR, Sada Jap P A, et al

Nat Commun. 2025;16(1):4621.

PMID: 40383826

Brief summary: This comprehensive study analysed immune cells from pancreatic, mesenteric, and splenic lymphatic tissues of autoantibody-negative individuals without T1D (ND), autoantibody-positive individuals (AAb+), and donors with type 1 diabetes (T1D). Decreased naïve T cells and increased cytotoxic NK cells were observed in the peripheral lymph nodes (pLNs) of individuals with T1D, along with a marked reduction in

CD25 expression on both $CD4^+$ and $CD8^+$ T cells. Additionally, decreased $CD4^+$ regulatory T cells (Tregs) were detected in the pLNs of antibody-positive individuals, even before T1D onset.

Autoimmune destruction of pancreatic β cells results in T1D, and evidence suggests that pancreatic lymph nodes (pLN) harbor immune cells that participate in this process (1). However, the immunological mechanisms occurring within human pancreas-draining lymphoid tissues remain poorly understood.

In this study, lymphoid immune perturbations were profiled in pLNs, mesenteric lymph nodes (mLNs), and spleens from a cross-sectional cohort of ND, AAb+, and T1D individuals. Deep immunophenotyping was performed using high-parameter flow cytometry ($n = 46$ donors) and cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq; $n = 18$ donors). In AAb^+ and T1D donor pLNs, a reduced frequency and increased instability of $CD4^+$ regulatory T cells (Tregs) were observed compared to ND pLNs, while memory $CD8^+$ T cells showed more pronounced stem-like characteristics. Increased differentiation of naïve T cells and NK cells was detected only in pLNs from T1D donors. In mLNs, alterations were limited to $CD4^+$ Tregs and naïve T cells, whereas few perturbations were noted in splenocytes.

Overall, the study identified significant immune perturbations occurring primarily within pLNs, both before and after the onset of T1D. In contrast, these changes were less pronounced in mLNs and absent in splenocytes. These findings emphasize the importance of pLNs as a key site for immune cell interactions and a potential future target for immunotherapies.

Reference

1. Sun F, Yang CL, Wang FX, *et al*. Pancreatic draining lymph nodes (PLNs) serve as a pathogenic hub contributing to the development of type 1 diabetes. Cell Biosci 2023;13(1):156.

10.14. Teplizumab induces persistent changes in the antigen-specific repertoire in individuals at risk for type 1 diabetes

Lledó-Delgado A, Preston-Hurlburt P, Currie S, Clark P, Linsley PS, Long SA, et al

J Clin Invest. 2024;134(18).
PMID: 39137044

Brief summary: The phenotypes, transcriptome, and repertoire of peripheral blood CD8+ T cells were analysed in individuals before and up to 18 months after a single 14-day course of teplizumab. At 3 months, activation signatures were observed in $CD4^+$ and $CD8^+$ T cells. By 18 months, responders showed reduced activation gene expression and increased markers of exhaustion and regulation. Unlike the placebo group, the frequency of autoantigen-reactive $CD8^+$ T cells did not expand with teplizumab.

Since November 2022, Teplizumab (an anti-CD3 monoclonal antibody) has been the first and only disease modifying drug approved by the Food and Drug Administration (FDA) for individuals with presymptomatic stage 2 type 1 diabetes (T1D) (individuals with 2 or more autoantibodies and dysglycemia) 8 years or older (1). The main trial which led to this approval was the TrialNet Teplizumab Prevention Study (TN10), a randomized placebo-controlled trial which showed that a single 14-day course of teplizumab caused a significant delay in progression to stage 3 T1D in people with presymptomatic stage 2 T1D, with 36% of participants remaining disease-free for over 5 years (2).

This study used single-cell RNA sequencing and reports detailed immunological analyses in peripheral blood cells from TN10 participants ($n = 68$), aiming to further understand the effects of teplizumab treatment and identify cellular signatures associated with long-term responses (up to 18 months) after a single course of the drug. The study showed an increase in transcriptomic signatures of $CD8^+$ T cell activation at 3 months post-treatment, followed by a decline and differentiation into effector cells with features of exhaustion and regulation by 18 months. Similar changes occurred in $CD4^+$ T cells, with initial activation and a subsequent decline in responders at 18 months. Teplizumab treatment also reduced the expression of IL7R in $CD8^+$ T cells, a receptor required for these cells' growth and expansion. Additionally, there was reduced expansion of autoantigen-reactive $CD8^+$ T cells in teplizumab- compared placebo-treated participants.

These data suggest that signals delivered by teplizumab affect multiple immune cell subsets, promoting the differentiation of $CD8^+$ T cells into regulatory and exhausted phenotypes, and preventing the expansion of autoantigen-specific $CD8^+$ T cells. These mechanisms may underlie the induction of operational tolerance following a single course of teplizumab treatment. Further studies comparing individuals protected from diabetes for extended periods with healthy controls may identify key immunological signatures associated with long-term tolerance.

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New Experimental Treatments

10.15. Harmine and extendin-4 combination therapy safely expands human β cell mass *in vivo* in a mouse xenograft system

Rosselot C, Li Y, Wang P, Alvarsson A, Beliard K, Lu G, et al

Sci Transl Med. 2024;16(755):eadg3456.
PMID: 38985854

Brief summary: In this experimental study, a combination of a dual tyrosine-regulated kinase 1A (DYRK1A) inhibitor (harmine) with a glucagon-like peptide 1 receptor agonist (GLP1RA) (extendin-4) increased *in vivo* human β-cell mass by 4- to 7-fold in both diabetic and nondiabetic mice over a 3-month period and reversed diabetes. The proposed mechanisms involved enhanced human β-cell proliferation, function, and survival.

Type 1 diabetes (T1D) is characterised by insufficient insulin-producing β-cells, and so far, no treatment is available to restore the β-cell numbers. Recent data suggest that small molecules that inhibit dual tyrosine-regulated kinase 1A (DYRK1A) can induce immunohistochemical markers of human β-cell replication, and this effect is enhanced by drugs that stimulate the glucagon-like peptide 1 (GLP1) receptor (GLP1R), such as extendin-4, on β-cells (1). It remains to be demonstrated whether these immunohistochemical findings translate into an increase in human β-cell numbers *in vivo*. It is also unknown whether DYRK1A inhibitors together with GLP1RA affect human β-cell survival.

To address these questions, human islets were transplanted under the kidney capsule of immunodeficient mice, both diabetic (streptozotocin induced) and non diabetic. These mice were treated for up to 3 months with either a vehicle control, the DYRK1A inhibitor harmine, the GLP1RA extendin-4 or a combination of harmine and extendin-4. β-cell mass and survival were quantified using 3D iDISCO imaging, which combines a tissue clearing technique with a light sheet microscopy approach. The combination of a DYRK1A inhibitor with extendin-4 resulted in a 4- to 7-fold increase in human β-cell mass compared to controls, in both diabetic and non diabetic mice over 3 months, and reversed diabetes. The augmentation in human β-cell mass occurred through mechanisms, including enhanced human β-cell proliferation, function, and survival.

Together, these findings demonstrate the therapeutic potential and favorable preclinical safety profile of the DYRK1A inhibitor-GLP1RA combination for increasing human β-cell mass *in vivo*. However, further studies are needed to elucidate the underlying mechanisms of action and to determine whether the therapeutic benefits and safety of this approach will translate to humans.

Reference

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11. Obesity and Weight Regulation

Martin Wabitsch[1], Julia Altvater Stephanie Brandt-Heunemann[1], Ayca Cimbek[2], Christian Denzer[1], Nicole Prinz[1], Melanie Schirmer[1], Lena Semelink-Sedlacek[1], Daniel Tews[1], Stefanie Zorn[1]

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Preface

In analogy to previous years, in this year's chapter we can present only 1% of the acquired publications (1,962) according to our search criteria in PubMed in the Yearbook 2025. The last year has again been extremely exciting for the field of obesity and weight regulation and the Yearbook chapter 2025 on obesity and weight regulation comprises selected articles of special interest to Paediatric Endocrinologists covering a broad research area.

The New Forecast is Worrying

11.1. Global, regional, and national prevalence of child and adolescent overweight and obesity, 1990-2021, with forecasts to 2050: a forecasting study for the global burden of disease study 2021

GBD 2021 Adolescent BMI Collaborators
Lancet 2025 Mar 8;405(10481):785-812.
PMID: 40049185. doi: 10.1016/S0140-6736(25)00397-6.
https://pubmed.ncbi.nlm.nih.gov/40049185/

Brief Summary: Using the established methods of the Global Burden of Diseases, Injuries, and Risk Factors Study 2021, this article presents modeled overweight and obesity rates for children and adolescents from 1990 to 2021 and generated forecasts extending through 2050. Between 1990 and 2021, the prevalence of both overweight and obesity rose markedly across all global regions, indicating that existing strategies to limit these increases have been largely ineffective. Projections beyond 2021 suggest that overweight rates during childhood and adolescence may plateau, primarily due to continued growth in obesity prevalence. Notably, obesity is anticipated to keep increasing across all populations and regions worldwide.

Historically, addressing undernutrition in young children has been a central focus for governments and donors across low- and middle-income countries. While continued investment in combating undernutrition remains essential, global nutrition priorities must now broaden to also address the rising prevalence of excess weight among children and adolescents in these countries. Low- and middle-income countries, in particular, face a limited timeframe during which investments targeting overnutrition can yield the greatest impact. Crucially, efforts to curb excess weight need not detract from undernutrition programs. These efforts demand multisectoral collaboration and comprehensive strategies that address the multifaceted drivers of obesity, including nutrition, physical activity, lifestyle, and environmental factors.

11.2. How obesity affects adipocyte turnover

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Trend in Endocrinology and Metabolism 2025 Feb, 36(2): 147-160.
PMID: 39095230 doi: 10.1016/j.tem.2024.07.004.
https://pubmed.ncbi.nlm.nih.gov/39095230/

Adipocyte turnover is a crucial process for maintaining adipose tissue homeostasis and metabolic flexibility. This review shows that this process is impaired in the obese state, leading to increased adipocyte death, inflammation and compensatory adipogenesis.

It had been hypothesized that the number of adipocytes is fixed during childhood [1,2]. That view had to be revised. The review provides a comprehensive overview on adipocyte turnover, particularly in the context of obesity. Unlike previous reviews which have focused only on isolated steps, either the adipocyte death, the adipocyte clearance or the generation of new adipocytes, this article summarizes current knowledge about the entire adipocyte turnover process – emphasizing how these steps are orchestrated, how they interplay in maintaining adipose tissue homeostasis and how important the roles of the immune system and inflammatory processes in adipose tissue homeostasis are. By linking impairments in adipocyte turnover like an excessive adipocyte death or a decreased adipogenesis, to metabolic dysfunctions like insulin resistance or inflammation, the review highlights the clinical importance of maintaining adipose tissue homeostasis. One part of the review discusses potential therapeutic strategies, like the selective removal of dysfunctional adipocytes, for example by using senolytic drugs to induce apoptosis of senescent cells or by using a specific type of immune cells, the invariant natural killer T-cells (iNKTs), to ameliorate metabolic complications.

Taken together, this review provides an excellent overview of the physiology and pathophysiology of adipocyte turnover, offering useful insights for both researchers and clinicians.

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11.3. Unveiling adipose populations linked to metabolic health in obesity

Reinisch I, Ghosh A, Noé F, Sun W, Dong H, Leary P, Dietrich A, Hoffmann A, Blüher M, Wolfrum C
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Cell Metab 2025 Mar 4;37(3):640-655.e4
doi: 10.1016/j.cmet.2024.11.006
https://pubmed.ncbi.nlm.nih.gov/39694039

Brief Summary: This study represents a major advance in the understanding of adipose tissue (AT) heterogeneity in the context of metabolic disease. By integrating single-nucleus RNA-sequencing (snRNA-seq) and bulk transcriptomics from both visceral (VAT) and subcutaneous (SAT) adipose depots in individuals with metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO), the study constructs a high-resolution cellular atlas of AT associated with health and disease states.

Traditional classification of obesity via BMI fails to distinguish individuals at differential risk of metabolic disease. This paper fills a critical gap by linking AT cellular composition and transcriptional programs to clinical phenotypes, providing mechanistic insight into why some individuals with obesity remain metabolically healthy. The study validates the hypothesis that adipocyte plasticity, rather than mass alone, is key to metabolic health. It confirms prior findings that VAT dysfunction, rather than total fat volume, is a major driver of insulin

resistance and other metabolic abnormalities [1,2]. The identification of mesenchymal-like mesothelial cells (meMesoCs) and their enrichment in metabolically healthy states is novel. It supports emerging literature suggesting that mesothelial cells are not inert but participate in epithelial-to-mesenchymal transition (EMT) and potentially in adipogenesis or immune modulation [3,4]. Further, the authors discovered a ZNF804B+ anti-adipogenic progenitor population (AAPs2), which is found only in MUO women and linked with adaptive immune recruitment. This adds a new layer to understanding sexual dimorphism in metabolic disease, complementing previous murine studies [5].

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11.4. Adipose tissue retains an epigenetic memory of obesity after weight loss

Hinte LC, Castellano-Castillo D, Ghosh A, Melrose K, Gasser E, Noé F, Massier L, Dong H, Sun W, Hoffmann A, Wolfrum C, Rydén M, Mejhert N, Blüher M, von Meyenn F

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Brief Summary: The study reveals that adipose tissue retains a persistent "epigenetic memory" of obesity, even after significant weight loss (WL), which primes adipocytes for dysfunctional responses to future obesogenic stimuli. Using multi-omics in both humans and mice, the researchers demonstrate that transcriptional and epigenetic changes in adipocytes—particularly histone modifications and enhancer activation—remain long after weight normalization, contributing to the common rebound weight gain seen after dieting.

While previous studies have documented improved metabolic function after WL, clinical data consistently show high rates of weight regain [1,2]. Hinte *et al.* demonstrate that adipocytes, APCs, and endothelial cells maintain transcriptional profiles indicative of prior obesity despite weight normalization. This confirms and extends the concept of *metabolic memory* [3], into the context of adipose tissue. The retention of histone marks such as H3K4me3, H3K27ac, and H3K27me3 at specific adipocyte promoters/enhancers (e.g., *IGF1*, *Gpam*, *PDE3A*) supports the existence of a durable epigenetic scar. A key insight is that weight-reduced adipocytes exhibit heightened glucose and palmitate uptake, aberrant lipid handling, and accelerated transcriptional responses to high fat diet, indicating a "*primed state"* even after normalization of body weight.

In the broader perspective, the authors uncover that adipocytes retain epigenetic scars from obesity that predispose individuals to relapse. This insight, built upon rigorous multi-omics and human–mouse comparative analyses, offers a robust molecular explanation for the clinical failure of many WL strategies and opens up new therapeutic avenues targeting the epigenome itself.

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In Utero Programming of Hippocampal Connectivity

11.5. Exposure to gestational diabetes mellitus in utero impacts hippocampal functional connectivity in response to food cues in children

Zhao S, Semeia L, Veit R, Luo S, Angelo BC, Chow T, Birkenfeld AL, Preissl H, Xiang AH, Page KA et al
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Brief Summary: This study examined the impact of gestational diabetes mellitus (GDM) exposure in 90 children age 7–11 years on hippocampal functional connectivity (FC) in response to food-related cues, utilizing functional magnetic resonance imaging (fMRI). Hippocampal FC was compared between children with and without GDM exposure. Compared to children without intrauterine exposure to GDM, children with exposure showed increased hippocampal FC in response to food cues, particularly with regions involved in reward processing.

The hippocampus plays a central role in learning and memory and is thought to contribute to the regulation of food intake by integrating past experiences with internal bodily signals [1]. Prior structural MRI findings have demonstrated reduced left hippocampal thickness in children prenatally exposed to GDM compared to non-exposed peers [2]. These observations suggest that GDM may influence both hippocampal structure and function.

The findings reported here indicate a specific impact of intrauterine exposure to (GDM) on hippocampal connectivity, predominantly involving reward-processing regions, rather than being attributable to obesity at this early age. These results are consistent with prior animal research [3, 4, 5] and lend support to the hypothesis that prenatal diabetes exposure may induce alterations in neural pathways.

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New Genes and their Pathogenicity

11.6. Loss of transient receptor potential channel 5 causes obesity and postpartum depression

Li Y, Cacciottolo TM, Yin N, He Y, Liu H, Liu H, Yang Y, Henning E, Keogh JM, Lawler K, Mendes de Oliveira E, Gardner EJ, Kentistou KA, Laouris P, Bounds R, Ong KK, Perry JRB, Barroso I, Tu L, Bean JC, Yu M, Conde KM, Wang M, Ginnard O, Fang X, Tong L, Han J, Darwich T, Williams KW, Yang Y, Wang C, Joss S, Firth HV, Xu Y, Farooqi IS
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https://pubmed.ncbi.nlm.nih.gov/38959890/

Brief Summary: This translational study identified microdeletions on chromosome Xq23 disrupting the *brain-expressed transient receptor potential channel 5* (*TRPC5*) in two unrelated boys with intense food-seeking behaviour, obesity, autism, anxiety, and maladaptive behaviour. These changes were shared with their mothers, who had obesity, anxiety, and postpartum depression. Analysis of exome data from the Genetics of Obesity Study cohort ($n = 984$) uncovered seven rare coding *TRPC5* variants in people with severe childhood-onset obesity, while data from the UK Biobank (~450,000) identified 369 variants in the general population linked to higher BMI. Generation of a knock-in mouse model with a human loss-of-function *TRPC5* mutation revealed that *TRPC5* regulates obesity, hyperphagia, maladaptive behaviour, and postpartum depression via hypothalamic proopiomelanocortin (POMC) and oxytocin (OXT) neurons.

Growing evidence suggests that innate or instinctive human behaviours fundamental for survival, such as food seeking, maternal care, self-preservation and socialization are genetically encoded by specific hypothalamic nuclei, though the exact mechanisms remain unclear [1,2]. This study identified microdeletions and rare variants in *TRPC5* in humans as potential cause for monogenic obesity and identified the first susceptibility loci for postpartum depression and impaired maternal care [3]. The observed phenotypic effects were found to be regulated by *TRPC5* via POMC and OXT neurons, providing new mechanistic insights into the regulation of obesity and postpartum depression. However, the study lacks detailed clinical characterization of affected individuals and their families to establish penetrance and mode of inheritance. While obesity and hyperphagia in *TRPC5* carriers may be treated with the MC4R agonist, setmelanotide, future research is needed to investigate wether OXT receptor agonists/analogs may restore *TRPC5* expression in OXT neurons, offering potential treatment for postpartum depression.

Taken together, these findings strongly support including *TRPC5* in diagnostic gene panels for severe childhood-onset obesity, autism, and postpartum depression, as treatment options may be available in the future.

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11.7. Variant reclassification over time decreases the level of diagnostic uncertainty in monogenic obesity: experience from two centres

Morandi A, Fornari E, Corradi M, Umano GR, Olivieri F, Piona C, Maguolo A, Panzeri C, Emiliani F, Cirillo G, Cavarzere P, Miraglia Del Giudice E, Maffeis C

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Pediatric Obesity. 2024; 19:e13183.

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Brief Summary: This multicenter observational study showed that the initial genetic variant evaluation uncertainty (overall 30 variants) and the molecular diagnostic uncertainty of monogenic obesity reduced by a third through genetic variant reassessment after three years of baseline classification. This achievement is due to advances in genomic data interpretation, including larger population datasets and knowledge of functional effects in monogenic obesity.

Accurate classification of genetic variants as possible causes for monogenic obesity is important for the diagnosis, for counselling of patients and for therapeutical management with access to new drug therapies. However, the molecular diagnosis of monogenic obesity is burdened by frequent variant uncertainty (e.g. variants of uncertain significance (VUS), likely benign or likely pathogen variants). Morandi *et al.* emphasize the dynamic of genetic interpretation and show the utility of ongoing variant reevaluation. Chen *et al.* recently

confirmed the necessity of uncertain variant reclassification in context of several rare diseases [1]. As manual adjustment is decisive for the meaningful interpretation of genetic variants and thus the increase of certain classifications (benign and pathogenic variants) a detailed patient phenotyping in monogenic obesity is essential. Guidelines concerning reevaluation frequency and exact method for performing the follow-up of variants should be elaborated for systematically reclassifiing previously identified variants.

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11.8. Unraveling the relationship between head circumference and MC4R deficiency from infancy to adulthood: a case-control study

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Brief Summary: This case-control study, including 63 children with *MC4R* deficiency (59 = monoallelic, $n = 4$ biallelic), found larger head circumference (HC) and taller height in *MC4R* carriers compared to the Dutch reference population and 63 age- and BMI-matched control children with multifactorial obesity. Macrocephaly was present in all children with biallelic variants ($n = 4$) and 36% of those with monoallelic variants ($n = 23$), compared to 25% in controls ($n = 16$). Interestingly, there was no difference in HC or height in *adult* monoallelic *MC4R* carriers ($n = 13$) compared to the Dutch reference population.

Identifying genetic variants in clinical practice is challenging due to the phenotypic heterogeneity between and within different forms of genetic obesity [1]. Although genetic testing has become standard in clinical practice and novel pharmacological therapies are available for certain forms of genetic obesity [2], widespread genetic testing remains limited by capacity. Therefore, specific phenotypic criteria are needed to identify individuals for genetic testing. The present study is crucial for clinical practice, as monoallelic *MC4R* variants are the most common form of genetic obesity, previously characterized by non-specific clinical features as severe childhood obesity, hyperphagia, and increased linear growth [3,4]. This study highlights that large HC is a specific clinical feature of *MC4R* carriers, associated with insulin resistance. However, the exact underlying mechanisms remain unclear and require further investigation. Furthermore, validation of these findings in larger or longitudinal paediatric and adult *MC4R* cohorts is necessary, along with investigating whether large HC is unique to *MC4R* variants or shared with other forms of monogenic obesity.

In summary, these findings suggest that regular HC measurements, particularly in children and adolescents, should be included in the screening of individuals with suspected monogenic obesity, as HC appears to be a key phenotypic characteristic of *MC4R* variant carriers.

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Diagnostic Lipid Profiling

11.9. Lipid profiling identifies modifiable signatures of cardiometabolic risk in children and adolescent with obesity

Huang Y, Sulek K, Stinson SE, Holm LA, Kim M, Trost K, Hooshmand K, Lund MAV, Fonvig CE, Juel HB, Nielsen T, Ängquist L, Rossing P, Thiele M, Krag A, Holm JC, Legido-Quigley C, Hansen T
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PMID: 39304782. doi: 10.1038/s41591-024-03279-x.
https://pubmed.ncbi.nlm.nih.gov/39304782/

Brief Summary: This cross-sectional study offers a significant contribution to pediatric metabolic research by using comprehensive lipidomics to identify early, modifiable biomarkers of cardiometabolic risk. In a cohort of 1,331 children (including 958 with overweight or obesity), the study found a distinct lipidomic signature that was strongly associated with insulin resistance, hepatic steatosis, and hypertension. Some associations not only persisted after adjusting for BMI, highlighting the added predictive value of lipid profiling, but also changed in response to a one-year family-based lifestyle intervention, demonstrating responsiveness to behavioural change. A specific 3-lipid panel predicted hepatic steatosis with high accuracy, rivalling or surpassing traditional liver enzyme tests.

This work builds on a growing body of adult literature linking ceramides and other lipid classes to metabolic and cardiovascular diseases [1-4]. However, few studies have translated these findings to pediatric populations [5-8]. Huang *et al.* bridge this gap by demonstrating that lipid profiles not only correlate with current metabolic risk but also change in response to lifestyle intervention.

Study strengths include its large sample size, advanced analytical techniques, and integration of both cross-sectional and longitudinal data. Limitations include lack of causal inference due to its observational design and limited demographic and ethnic diversity. Nonetheless, it advances the field by identifying modifiable lipid signatures with potential as early indicators and therapeutic targets. Future research should focus on validating these biomarkers in more diverse populations and integrating them into clinical screening protocols.

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Innovative Interventions

11.10. A digital health behavior intervention to prevent childhood obesity – the greenlight plus randomized clinical trial

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JAMA. 2024;Dec 24;332(24):2068-2080.
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Brief Summary: There remains an urgent need for practicable and effective childhood obesity prevention strategies. This multicenter randomized parallel-group trial, involving 900 newborns and their families, evaluated a digital health behavior intervention (automated tailored text messages plus web-based dashboard) alongside standard pediatric counseling ("clinic + digital", $n = 449$) vs counseling alone ("clinic-only", $n = 451$). Over 24 months (~15% lost-to-follow-up per group), children in the digital intervention group showed healthier weight-for-length trajectories (mean reduction: –0.33 kg/m [95% CI: –0.57 to –0.09]) and lower BMI z-scores (–0.19 [95% CI: –0.36 to –0.01]). Effects emerged by 4 months and were most pronounced in food-insecure families. Obesity rates (CDC) at 24 months were 7.4% vs. 12.7% (adjusted risk ratio: 0.56 [95% CI: 0.36 to 0.88]).

The study, with robust design and a low-cost scalable digital tool, underscores the effectiveness of early-life prevention strategies in improving weight outcomes during the first 2 years of life, particularly in underserved populations. Intervention starting in the first weeks of life is a time-fame, when many obesity-related habits begin [1,2]. Long-term sustainability remains uncertain, especially if diverse external influencing factors (e.g. peer group) emerge in later life. Nonetheless, rapid weight gain within the first 3 months of life has been linked to future cardiovascular risk [3], supporting the importance of early intervention. Study limitations include lack of data on dashboard use or isolated effects of text messaging vs. dashboard, and limited generalizability (English-/Spanish speaking families from the US with smartphones). On average only 54% responded to the text messages. No information on length is provided although growth impairment is one concern in children living with obesity. Nevertheless, the findings support high potential for broad implementation in pediatric primary care.

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11.11. Long-term results of a digital treatment tool as an add-on to pediatric obesity lifestyle treatment: a 3-year pragmatic clinical trial

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Brief Summary: The effect of evidence-based behavior intervention programs on childhood obesity remission is limited [1]. Best results could be seen with contact hours ≥ 26/year [2]. However, this is often difficult to achieve for both families and health care providers due to time and resource constraints. This 3-year, pragmatic, single-center trial among 428 children evaluated the effectiveness of *Evira*, a digital tool paired with physical visits ("digi-physical" care, $n = 107$), as an add-on to standard pediatric obesity treatment ($n = 321$). After 3 years, the digi-physical group had greater BMI z-score reduction (–0.29 [95%CI: -0.40, -0.18] vs. -0.12 [-0.21, -0.03], $P = 0.02$) and higher obesity remission rates (31.8% vs. 18.7%, $P = 0.005$), with even more pronounced effects in a subset of adolescents ($n = 50$).

Evira is a modern attractive individualized mobile health technology with regular home measurements presented only as a visual (non-numerical) trend in BMI Z-score, with data transfer and messaging with the clinic. Addition of such a digital tool to physical visits is highly promising regarding sustained weight loss over 3 years, without weight regain as often known from standard care. Moreover, the well-established challenging

treatment adherence improved by the digital tool. The study highlights the value of digital data-driven feedback in addition to motivational interviewing over traditionally prescriptive advice to increase parental empowerment. However, long-term sustainability beyond 3 years of digi-physical treatment must be studied, as overall attrition and engagement declined over time (e.g. home weighing frequency dropped from 3.9 to 2.9 times/week by year 3). Further, multicenter trials with larger, diverse populations and standardized lifestyle factor assessment (e.g. diet, sleep, stress) are needed to confirm long-term generalizability. The current plans for wider use of *Evira* in commercial settings, international clinical trials and in combination with weight loss medication is more than welcome to potentially overcome limitations of behavior intervention programs on childhood obesity so far. Recently, *Evira* has been commissioned by the UK National Health Service.

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11.12. Liraglutide for children 6 to $<$12 years of age with obesity — a randomized trial

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Brief Summary: This phase 3 trial demonstrated that in children aged 6 to under 12 years with obesity, 56 weeks of liraglutide (target dose: 3.0 mg/d) combined with lifestyle intervention reduced BMI compared to placebo plus lifestyle changes.

The GLP-1 receptor agonists liraglutide and semaglutide are currently approved for long-term weight management in adolescents aged $\geq$12 years with obesity, in combination with lifestyle modifications. Their mechanisms involve enhancing satiety, reducing appetite and caloric intake, and dampening food reward, as well as promoting postprandial insulin secretion, suppressing glucagon, and delaying gastric emptying. However, no pharmacological treatments have been approved for non-monogenic, non-syndromic obesity in children under 12 years of age.

This study thus marks a major milestone and will likely pave the way for extending liraglutide approval to children as young as 6 years. Notably, although caution is needed when comparing across different age groups and study designs, the observed greater BMI reduction in younger children here (vs effects in adolescents from previous studies) suggests possible advantages of earlier intervention [1].

These findings support the hypothesis that younger children may respond more favourably to obesity interventions, as also indicated in lifestyle-based studies [2,3]. Introducing pharmacologic therapy at a younger age could potentially alter disease trajectory and prevent the entrenchment of obesity-related metabolic and psychosocial comorbidities. Future long-term data will be crucial to confirm durability, safety, and impacts on quality of life.

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11.13. Setmelanotide in patients aged 2–5 years with rare MC4R pathway-associated obesity (VENTURE): a 1 year, open-label, multicenter, phase 3 trial

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Lancet Diabetes Endocrinol. 2025 Jan;13(1):29-37.
PMID: 39549719. doi: 10.1016/S2213-8587(24)00273-0.
https://pubmed.ncbi.nlm.nih.gov/39549719/

Brief Summary: This open-label, phase 3, multicenter trial evaluated setmelanotide in 12 children aged 2–5 years with rare genetic obesity (POMC or LEPR deficiency or Bardet-Biedl syndrome). After 52 weeks, 83% achieved a meaningful reduction in BMI z-score, with improvements in hunger and caregiver burden, supporting early targeted intervention.

The VENTURE trial is the first to assess setmelanotide in children under 6 years with severe early-onset obesity due to MC4R pathway deficiencies or Bardet-Biedl syndrome, addressing an urgent need for effective early treatment. In POMC or LEPR deficiency, severe early-onset obesity driven by hyperphagia progresses rapidly, with annual weight gain over 7 kg despite intensive lifestyle or surgical interventions, underscoring the limitations of traditional approaches [1].

Setmelanotide, an MC4R agonist, has shown substantial efficacy in older patients, and this study extends those benefits to very young children, with a mean BMI reduction of 18% overall and significant hunger improvement reported by 91% of caregivers. The favourable safety profile and reduction in caregiver burden are particularly relevant given the psychosocial strain often experienced by these families.

Although the open-label design and small cohort limit generalizability, these findings suggest that early pharmacologic intervention can meaningfully alter the natural course of severe genetic obesity, potentially mitigating long-term metabolic and psychosocial complications. Future studies in larger and more diverse cohorts are needed, but the present work already represents a significant advance in precision medicine for rare forms of pediatric obesity.

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Long-Term Benefits of Bariatric Surgery in Adolescents

11.14. Ten-year outcomes after bariatric surgery in adolescents

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https://pubmed.ncbi.nlm.nih.gov/36443241/

Brief Summary: The prospective, multicenter observational cohort study "Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS)" included 260 adolescents (aged 13-19 years) undergoing bariatric surgery. Both Roux-en-Y gastric bypass and sleeve gastrectomy resulted in sustained weight loss (−20%; 95% CI: −22.9 to −17.1) and long-term remission of key obesity-related comorbidities over a 10-year period.

The Teen-LABS cohort [1] provides critical long-term evidence supporting the efficacy and durability of bariatric surgery in adolescents with severe obesity. In this prospective, multicenter cohort, of 260 participants, adolescents undergoing either Roux-en-Y gastric bypass or sleeve gastrectomy achieved substantial and sustained reductions in BMI (mean −20%; 95% CI: -22.9 to -17.1), with similar trajectories observed across both procedures. Latent class analysis identified distinct patterns of weight change, with greater early

postoperative weight loss emerging as a strong predictor of long-term success. Beyond weight reduction, the study demonstrates durable remission of major obesity-related comorbidities. At 10 years, remission rates were 55% for type 2 diabetes, 57% for hypertension and 54% for dyslipidemia. Notably, the remission rate for type 2 diabetes exceeded those reported in adult cohorts [2], underscoring the potential metabolic advantages of earlier surgical intervention.

These findings support the concept that bariatric surgery may meaningfully alter the progression of obesity-related disease. The study's strengths include its prospective design, standardized methodology, and excellent follow-up (>90%) across multiple centers. However, limitations, such as the absence of a non-surgical control group and limited statistical power for certain comorbidity outcomes, should be considered when interpreting the results.

Teen-LABS provides compelling evidence for the integration of bariatric surgery into structured, guideline-based obesity care in adolescents.

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11.15. Functional mobility and pain are improved for 6 years after adolescent bariatric surgery

Thivalapill N, Jenkins TM, Inge TH, Xie C, Courcoulas AP, Harmon CM, Helmrath MA, Sisley S, Michalsky MP, Ryder JR
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Obesity (Silver Spring). 2025 Jun;33(6):1126-1135.
doi: 10.1002/oby.24285 https://pubmed.ncbi.nlm.nih.gov/40259728/

Brief Summary: Metabolic and bariatric surgery (MBS) is known to offer improvement in functional mobility and musculoskeletal pain in the short term, but the durability of the effects in the long term and in the setting of weight regain are unknown. The prospective, multicenter observational cohort study Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) followed 205 adolescents (aged 13 to 19 years) for up to 6 years after metabolic and bariatric surgery. Sustained improvements in functional mobility and walking-related musculoskeletal pain were observed, despite modest weight regain.

Adolescents with severe obesity are at elevated risk for mobility limitations and musculoskeletal pain [1,2], both of which significantly impair participation in physical activity and overall quality of life[2]. The Teen-LABS cohort study offers longitudinal data demonstrating that MBS yields sustained improvements in these functional domains over a six-year follow-up period. Notable findings include a significant reduction in 400-meter walk time, improved post-exercise heart rate recovery, and a substantial decrease in self-reported musculoskeletal pain, effects that persisted even in individuals who experienced partial weight regain. The mediation analysis indicates that several observed benefits, such as reductions in immediate post-exercise heart rate and musculoskeletal discomfort, were mediated by weight-independent mechanisms. This suggests that physiological factors beyond weight loss itself, such as decreased systemic inflammation or altered biomechanical load distribution, may play a critical role in functional improvement after MBS. These findings underscore the long-term functional benefits of MBS during adolescence and emphasize the complex interplay between body weight, physiological adaptations, and physical function. Further research into the underlying biological mechanisms responsible for these weight-independent effects could inform the development of novel therapeutic strategies, both surgical and non-surgical, aimed at enhancing physical function and reducing pain in adolescents with severe obesity.

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Long-term Benefits of Pediatric Obesity Treatment

11.16. Effect of pediatric obesity treatment on long-term health

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JAMA Pediatr. 2025 Mar 1;179(3):302-309.
PMID: 39836390. doi: 10.1001/jamapediatrics.2024.5552.
https://pubmed.ncbi.nlm.nih.gov/39836390/

Brief Summary: This large-scale Swedish cohort study investigated how effective paediatric obesity treatment impacts long-term health outcomes in adulthood. The researchers followed over 6,700 children and adolescents (ages 6–17) who had received behavioral-based obesity treatment for at least 1 year. The study analysed the health outcomes as young adults (ages 18–30) and compared them with over 32,000 matched controls. The primary finding was that effective obesity treatment during childhood reduces the risk of serious health complications in adulthood.

Long-term data on the effect of childhood obesity treatment on adulthood are rare, making the present study particularly important given the increasing number of affected children [1,2]. This study adds important evidence: children who achieved obesity remission after treatment had an 86% lower risk of early death, compared to those with poor treatment response. They also had reduced risks of developing type 2 diabetes (HR 0.16), hypertension (HR 0.40) and dyslipidemia (HR 0.22). Participants with a "good response" to treatment (BMI SDS reduction >0.25 without remission) also experienced substantial health benefits and even intermediate responders (BMI SDS reduction -0.24 - +0.24) had better outcomes than poor responders (BMI SDS increase >0.25). Children aged 6–11 were more likely to achieve remission or a good response (~48%) compared to adolescents aged 12–17 (~29%). Interestingly, despite physical health improvements, the study found no impact on adult mental health outcomes like depression or anxiety.

Altogether, the study provides strong evidence that paediatric obesity treatment, particularly when started early and resulting in significant BMI reduction, can substantially lower the risk of chronic disease and early death in adulthood. It emphasizes the importance of early, structured treatment efforts involving family-based behavioural-based approaches and calls attention to the gap in mental health outcomes [3]. However, a critical examination of the numbers reveals that even if childhood obesity resolved, the incidence of comorbidities remains elevated compared to the general population; in the case of type 2 diabetes, the incidence is even 4-times higher. Therefore, preventing the development of obesity is also of great importance.

Key strengths of the study include its large sample size, long follow-up period, and real-world treatment settings. However, limitations include the non-randomized design and lack of standardized treatment protocols, making it difficult to isolate the most effective interventions. Overall, the study adds high-quality evidence in favour of pediatric obesity treatment as a long-term investment in public health.

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11.17. Hypothalamic obesity: from basic mechanisms to clinical perspectives

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Lancet Diabetes Endocrinol. 2025 Jan;13(1):57-68.
doi: 10.1016/S2213-8587(24)00283-3. https://pubmed.ncbi.nlm.nih.gov/39547253/
Erratum in: Lancet Diabetes Endocrinol 2025 Jan;13(1):e1.
doi: 10.1016/S2213-8587(24)00368-1. PMID: 39547253.

Brief Summary: This review covers the pathogenesis, diagnosis and treatment of hypothalamic obesity, and also presents the latest advances and new approaches for the management of these rare forms of obesity.

Perturbation of circuits in the hypothalamus, the primary regulator of body weight and energy homeostasis, can contribute to the development of obesity. Monogenic obesity syndromes, characterized by early onset and severe obesity, impair the function of these circuits. Most genetic variants known to cause monogenic obesity so far affect the leptin-melanocortin pathway [1] The authors describe the hypothalamic control of body weight through the fundamental nuclei and neuronal circuits, as well as other homeostatic systems and non-neuronal pathways. It was also shown that methylation in a variably methylated region in the *POMC* gene was associated with individual body weight [2]. Hypothalamic obesity mostly develops as a result of acquired causes, central nervous system tumors being the most common reason.

Patients with hypothalamic obesity demonstrate findings such as hyperphagia, diminished sympathetic activity, low metabolic rate and decreased voluntary physical activity. Management of these disorders should comprise multicomponent interventions, involving multidisciplinary teams. Weight reduction through lifestyle intervention is hardly possible. Findings suggest that setmelanotide and new GLP-1 receptor agonists may be effective for weight loss in these patients. Bariatric surgery was shown to be effective and relatively safe in the treatment of patients with obesity and craniopharyngioma [3]. Future research programmes using patient-derived stem cell-based model systems and single-cell methylome studies will elucidate in more detail the pathophysiology and treatment targets of hypothalamic obesity.

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12. Type 2 Diabetes, Metabolic Syndrome and Lipid Metabolism

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Type 2 Diabetes

12.1. Childhood maltreatment, adulthood obesity and incident type 2 diabetes: a retrospective cohort study using UK biobank

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Int J Obes (Lond). 2025 Jan;49(1):140-146.

doi: 10.1038/s41366-024-01652-x

Brief Summary: In a large retrospective cohort analysis, UK Biobank study participants recalled childhood maltreatment. Individuals reporting childhood maltreatment, especially those with ≥ 3 types, had higher risks of adult obesity and incident T2D.

Comment: Recent data from the SWEET study[1] revealed that over the last decade there has been a global twofold increase in the proportion of T2D diagnoses among children and adolescents. In North America and Australia, approximately 14% of new pediatric diabetes cases are now classified as T2D.

Concurrently, a growing body of research has underscored the long-term health consequences of early-life adversity. Childhoodmal treatment - which encompasses physical, sexual, verbal, and emotional abuseas well as emotional neglect - is alarmingly common. In high in come countries, an estimated **7%** of children experience physical abuse and 11% endure emotional neglect.

The current retrospective cohort study examined the association between childhood maltreatment and the risk of obesity and T2D in adulthood. The analysis included 150,000 adults from the general population (mean age 55 ± 8 years) who completed an online questionnaire incorporating the Childhood Trauma Screener to assess maltreatment history. Overall, 33% reported at least one form of maltreatment and 13% reported multiple types of maltreatment. Emotional neglect was the most reported (22%), followed by emotional abuse (9%) and sexual abuse (9%).

Individuals with a history of childhood maltreatment were more likely to be younger, female, smokers, and less likely to have a college degree. Importantly, they were also more likely to be obese, and more likely to have T2D. Those reporting 3 or more types of childhood maltreatment had a 55% higher likelihood of adult obesity, and a 65% higher risk of developing T2D compared to individuals without a history of maltreatment. Stress-related overeating and depression are potential mediators linking childhood maltreatment to obesity.

Key Message: In children with severe obesity, clinicians should maintain a heightened awareness of the potential for abuse, particularly when other warning signs are present. In adults with obesity and T2D, it is essential to assess for a history of childhood maltreatment.

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12.2. Suicide risk screening in a diverse cohort of youth with type 1 and type 2 diabetes

Fatima S, Prichett L, Campbell N, Snyder MCN, Bifano M, Wolf RM
Pediatr Diabetes. 2025 Jun 2;2025:6662248.
doi: 10.1155/pedi/6662248

Brief summary: This prospective study assessed suicide risk screening in pediatric patients with diabetes by administering the Patient Health Questionnaire-(9 PHQ-9) and Ask Suicide-Screening Questions (ASQ) surveys during routine visits at a tertiary pediatric diabetes center.

The aim of this study was to determine the prevalence of suicide risk among adolescents with type 1 (T1D) and type 2 diabetes (T2D) and to evaluate the diagnostic accuracy of 2 screening tools: the PHQ-9), which includes 8 items on depressive symptoms and 1 item on suicide risk, and the ASQ, a brief 4-item yes/no questionnaire.

309 adolescents were included, 237 with T1D (mean age 14.8 years) and 72 with T2D, (mean age 16.1 years). Among those with T2D, 23.6% had a diagnosis of ADHD, 27.8% had depression, 33.3% were under the care of a regular behavioral health provider, 41.2% were prescribed psychotropic medications, and 48.6% had a family history of mental health disorders. Overall, 50% of adolescents with T2D reported depressive symptoms.

Compared to adolescents with T1D, those with T2D had nearly twice the rate of documented mental health diagnoses (45.8% vs. 25.3%) and PHQ-9–screened depression (50% vs. 27.8%), as well as more than double the rate of suicide risk identified by the ASQ (19.4% vs. 8.4%). Suicide risk was approximately twofold higher in adolescents with T2D than in those with T1D, based on both PHQ-9 Item 9 (12.5% vs. 5.9%) and the ASQ (19.4% vs. 8.4%).

Key Message: Adolescents with T2D exhibit high rates of depression and suicidal ideation. Relying solely on PHQ-9 Item 9 is insufficient for detecting suicide risk; using a dedicated screening tool like the ASQ is recommended for accurate identification of at-risk youth.

Transition to Adult Care: Yet Another Challenge for Adolescents with Type 2 Diabetes

12.3. Navigating transition to adult care in youth-onset type 2 diabetes: facilitators, attitudes, barriers, and behaviors

Glaros SB, Dixon SD, Malandrino N, Davis FS, Chowdhury A, Kacker IA, Macheret NA, Cantor SL, Thota G, Mabundo L, Gordon CM, Lightbourne M, Estrada DE, Monaghan M, Chung ST
J Clin Endocrinol Metab. 2025 Apr 15:dgaf239.
doi: 10.1210/clinem/dgaf239

Brief Summary: This cross-sectional single center cohort study assessed 65 youth with T2D as they transitioned from pediatric to adult carein the diabetes clinic at the National Institutes of Health (NIH) Clinical Center between January 2021 and December 2024. The multidisciplinary transition team included a pediatric endocrinologist, an internal medicine/pediatric endocrinologist, an adult endocrinologist, a psychologist, dieticians, a pharmacist, a certified diabetes care and education specialist, and a clinical research coordinators/patient navigator. The clinic integrates participants into an adult-care model without changing clinicians. Despite this comprehensive setup, 95% of participants reported significant psychosocial challenges, including stress, socioeconomic hardship, and mood symptoms, which were linked to reduced transition readiness.

Comment: There has been growing interest in the role of pediatric-to-adult transitional care in improving health outcomes among children and young adults with pediatric-onset chronic conditions.[1] While factors that promote or impede the transition of diabetes care in youth with type 1 diabetes are well described, much less is known about the transition of care in youth with T2D. Considering the rising incidence of early-onset T2D and the importance of a successful transition from pediatric to adult care for ensuring positive long-term outcomes, this article is both timely and important.

Based on the Six Core Elements of Health Care Transition[2]—which identify age 14 as the starting point for assessing transition readiness, given that adolescents at this age exhibit decision-making patterns similar to those of young adults, although emotional regulation, motivation, and behavioral control may continue to develop until age 24—the eligible population included adolescents and young adults aged 14 to 24 years.

These findings indicate a widespread lack of readiness for transition. Major perceived obstacles included difficulty scheduling specialist appointments, transportation barriers, challenges navigating insurance coverage, managing diabetes self-care when ill, and handling prescriptions. Notably, 68% of participants reported social, emotional, and cognitive challenges; more than 50% were worried about their future, approximately 40% reported frequent sadness and attention difficulties, 46% reported feeling burdened by diabetes, 25% experienced diabetes "burnout," and 15% felt unable to keep their blood sugars in range and reported that diabetes care interfered with daily activities. Mood symptoms were associated with a nearly tenfold increase in the likelihood of experiencing mild cognitive challenges, such as forgetfulness and poor attention. These findings align with previous report from the SEARCH study, which indicated that 29% of youth with T2D did not transition to adult care and 15% reported receiving no care at all.[3]

Key message: This timely study sheds light on the understudied experiences of youth with T2D during healthcare transition. It underscores the urgent need for personalized, multidisciplinary interventions to optimize care continuity in this vulnerable population.

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12.4. Insulin clearance at randomisation and in response to treatment in youth with type 2 diabetes: a secondary analysis of the TODAY randomised clinical trial

Nadeau KJ, Arslanian SA, Bacha F, Caprio S, Chao LC, Farrell R, Hughan KS, Rayas M, Tung M, Cross K, El Ghormli L, TODAY Study Group

TODAY Study Group.

Diabetologia. 2025 Mar;68(3):676-687.

doi: 10.1007/s00125-024-06327-w

Brief Summary: This paper presents a secondary analysis of the U.S. TODAY randomized clinical trial, evaluating insulin clearance (IC) in 640 youth with T2D, highlighting differences by sex, race/ethnicity, and response to treatments (metformin alone, metformin plus lifestyle intervention, or metformin plus rosiglitazone). IC was lower in females compared to males, and notably lower IC among non-Hispanic Black youth compared with Hispanic and non-Hispanic White youth. Lower IC correlated with higher obesity, insulin resistance, and lower adiponectin concentrations over 5 years. Treatment with metformin plus rosiglitazone increased IC, an effect largely attributable to improvements in adiponectin and insulin sensitivity, whereas lifestyle intervention showed minimal impact.

Comment: Insulin clearance (IC) is the rate at which insulin is removed from circulation, primarily mediated by the liver (via first-pass extraction). In obesity, IC is typically reduced through a direct effect of insulin sensitivity on clearance, contributing to hyperinsulinemia. In T2D, IC is further reduced, associated with both hepatic steatosis and worsening glycemic control. The saturable nature of hepatic insulin extraction means that at high rates of insulin secretion (as seen in insulin-resistant states), the liver's capacity to clear insulin plateaus, leading to increased systemic insulin levels. Lower IC has been consistently associated with obesity, insulin resistance, increased visceral fat, and hepatic steatosis. Furthermore, significant differences in IC have been observed by sex and ancestry, with lower IC among females and individuals of non-Hispanic Black background.

This secondary analysis reports that IC is notably lower among non-Hispanic Black youth, aligning with findings in adults and the known increased metabolic risk in this population. The improvement in IC with rosiglitazone suggests the metabolic benefits of enhancing adipose tissue function and insulin sensitivity through pharmacological intervention, while lifestyle intervention alone was insufficient. These findings confirm that T2D in youth is an aggressive metabolic disorder requiring tailored and aggressive treatment strategies, especially for those from high-risk demographic groups.

Key Message: Insulin clearance is low in female and non-Hispanic Black youth with T2D and is closely linked to obesity, insulin resistance, and dysmetabolism. Reduced IC contributes to hyperinsulinemia, which further exacerbates insulin resistance and β-cell stress, perpetuating metabolic disturbances. While IC does not directly predict glycemic outcomes, interventions improving insulin sensitivity, particularly with pharmacotherapy, effectively enhance IC and metabolic health.

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12.5. Dulaglutide and glomerular hyperfiltration, proteinuria, and albuminuria in youth with type 2 diabetes: post hoc analysis of the AWARD-PEDS study

Bjornstad P, Arslanian SA, Hannon TS, Zeitler PS, Francis JL, Curtis AM, Turfanda I, Cox DA

Diabetes Care. 2024 Sep 1;47(9):1617-1621.
doi: 10.2337/dc24-0322

Brief Summary: Thispaper reports a post hoc analysis of the AWARD-PEDS study, evaluating the effects of dulaglutide on kidney function in youth aged 10–18 years with T2D. AWARD-PEDS enrolled 154 youth aged 10 to $<$18 years with T2D andBMI $>$85th percentile. Participants were either on metformin, with or without basal insulin, or following lifestyle modification alone, and were randomized to receive dulaglutide (0.75 mg or 1.5 mg once weekly) or placebo. The cohort was ~50% female and included individuals of diverse ancestry, reflecting the epidemiology of pediatric T2D in the United States. The primary outcome was the change in HbA1c at 26 weeks. Dulaglutide reduced HbA1c by 0.6–0.9 percentage points compared to a 0.6 percentage point increase with placebo. More dulaglutide-treated participants achieved HbA1c $<$7.0% (51% vs. 14% with placebo). There was no difference in BMI change between the groups.

In this post hoc analysis over 26 weeks, dulaglutide was associated with a reduction in estimated glomerular filtration rate (eGFR) compared to placebo, particularly in those with baseline glomerular hyperfiltration. Additionally, the prevalence of both glomerular hyperfiltration and proteinuria decreased in the dulaglutide group, whereas these measures increased in the placebo group. The study did not establish whether these changes translate into a reduced long-term risk of diabetic kidney disease in this population.

Comment: In adults with obesity, renal hyperfiltration (increased glomerular filtration rate (GFR) relative to body weight) is associated with early kidney injury, as evidenced by increased albuminuria. The pathophysiology involves increased renal plasma flow and intraglomerular hypertension, driven by afferent arteriolar vasodilation, insulin resistance, and activation of the renin-angiotensin-aldosterone system. This leads to glomerular and tubular hypertrophy, increased Bowman's space, and, over time, proteinuria, microalbuminuria, and progression to focal segmental glomerulosclerosis and chronic kidney disease. In adolescents with obesity, renal hyperfiltration is highly prevalent, depending on the definition and GFR estimation method used. In adolescents, hyperfiltration is associated with insulin resistance, hypertriglyceridemia, and hyperuricemia, and may be an early marker of obesity-related glomerulopathy. Adolescents with hyperfiltration often have a worse cardiometabolic profile and are at increased risk for future CKD. Therefore, early identification and interventions are critical to prevent progression to irreversible kidney damage and

associated metabolic complications in youth with obesity and T2D. This secondary analysis supports the principle that pharmacologic intervention to improve glucose metabolism and/or promote weight loss may be an important component of management of risk for kidney disease in adolescents with obesity and T2D.

Key Message: In adolescents, obesity and T2D are associated with glomerular hyperfiltration, which is a risk for early development of CKD. Therefore, comprehensive management of these adolescents requires early identification and management of hyperfiltration. In addition to current efforts at improving lifestyle and weight, this manuscript provides support for pharmacologic interventions to improve glucose control, insulin resistance, and adiposity.

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Youth Onset T2D and Pregnancy

12.6. Perinatal outcomes associated with metformin use during pregnancy in women with pregestational type 2 diabetes mellitus

Yland JJ, Huybrechts KF, Wesselink AK, Straub L, Chiu YH, Seely EW, Patorno E, Bateman BT, Mogun H, Wise LA, Hernández-Díaz S

Diabetes Care. 2024 Sep 1;47(9):1688-1695.
doi: 10.2337/dc23-2056

Brief summary: This observational study analysed U.S. healthcare claims data and applied *target trial emulation methods* to assess the safety of continuing metformin during pregnancy in women with T2D. By mimicking the design of a randomized controlled trial, it found that continuing metformin was not associated with an increased risk of adverse neonatal outcomes.

Comment: With the rising burden of the T2D epidemic at younger ages, an increasing number of pregnancies in young women with T2D is expected. Previous data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study reported 260 pregnancies among 141 women (mean age 21.5 $\pm$ 3.2 years, BMI 35.6 $\pm$ 7.2 kg/m^2, and diabetes duration 8.1 $\pm$ 3.2 years). Pregnancy complications occurred in 65% of women, including pregnancy loss in 25% and preterm birth in 32.6% of cases.[1] Among the offspring, 7.8% were classified as small for gestational age, 26.8% as large for gestational age, and 17.9% were macrosomic.

Two randomized trials (MiTy and MOMPOD)[2,3] evaluated the addition of metformin to insulin therapy in pregnant women with pregestational T2D. While metformin modestly improved glycemic control, no difference in composite perinatal outcomes was observed.

The current study assessed the safety of continuing metformin treatment during pregnancy in a real-world setting, including 2,255 pregnant women with T2D, 597 who continued metformin during pregnancy and 1,658 who discontinued treatment. The primary outcome was a composite of adverse neonatal events, including preterm birth, birth injury, neonatal respiratory distress, neonatal hypoglycemia, and neonatal intensive care unit admission.

Continuing metformin in women with T2D who were previously treated with metformin plus insulin was not associated withan increased risk of a composite adverse neonatal outcomes compared with remaining on insulin alone. However, in a subgroup of commercially insured women, a twofold increased risk of SGA was observed - a finding not replicated in the publicly insured cohort. This increased risk of SGA may be due tometformin crossing the placenta, potentially exerting a direct in utero effect on fetal growth. In addition, other possible mechanism, include an effect of metformin on maternal diet, reduced weight gain during pregnancy, cell growth,

folate-related pathways, and/or placental function. The discrepancy between subgroups may reflect differences in adherence, as well as clinical and demographic characteristics across cohorts.

Key message: Continuing metformin during pregnancy does not appear to increase the risk of adverse neonatal outcomes and does not necessitate discontinuation. However, a potential association with increased SGA risk warrants close monitoring of fetal growth in women with pregestational diabetes who continue metformin treatment.

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Review of the Year

12.7. Early-onset type 2 diabetes: the next major diabetes transition

Luk A, Wild SH, Jones S, Anjana RM, Hivert MF, McCaffrey J, Gregg EW, Misra S
Lancet. 2025 Jun 28;405(10497):2313-2326.
doi: 10.1016/S0140-6736(25)00830-X

Brief Summary: This paper highlights the alarming global rise in early-onset T2D, encompassing youth-onset (<18 years) and young-adult onset T2D (<40 years). It explores the multifactorial causes, including obesity, socioeconomic disadvantages, ethnicity, genetics, and early-life exposures, with an emphasis on the rapid disease progression, increased complications, and substantial health burden associated with early-onset T2D.

Comment: This first paper in a 3-part *Lancet* Series[1,2] provides a comprehensive overview of the epidemiology and risk factors driving the global rise of early-onset T2D. The authors present compelling evidence that early-onset T2D, encompassing youth-onset and young-adult onset, is no longer rare and is becoming a defining feature of the modern diabetes epidemic.

The authors emphasize major changes in the global landscape of T2D over recent decades. While T2D was once primarily a concern in high-income countries, a rapid rise is now observed worldwide, including in low- and middle-income countries. Early-onset T2D is particularly concerning, due to its longer duration across the lifespan and more aggressive clinical course, with higher rates of both microvascular and macrovascular complications.

Obesity remains the leading risk factor, but the threshold for developingT2D varies by ethnicity. Socioeconomic status plays a dual role. In high-income countries, early-onset T2D disproportionately affects lower-income groups, while in low- and middle-income countries rising affluence and urbanization contribute to increased risk. Prenatal factors, such as in utero exposure to maternal diabetes or undernutrition, may increase future risk of T2D through epigenetic programming, contributing to a vicious cycle of intergenerational metabolic risk. The authors advocate for better surveillance, earlier screening, ethnicity-specific definitions, and life-course approaches to prevention.

Key message: This article, along with the 2 subsequent papers on early-onset T2D, represents a crucial and timely contribution to our understanding of the evolving diabetes epidemic. Together, these papers effectively integrate global data, biological insights, socioeconomic perspectives, complications, and treatment approaches.

12.8. Retrograde mitochondrial signaling governs the identity and maturity of metabolic tissues

Walker EM, Pearson GL, Lawlor N, Stendahl AM, Lietzke A, Sidarala V, Zhu J, Stromer T, Reck EC, Li J, Levi-D'Ancona E, Pasmooij MB, Hubers DL, Renberg A, Mohamed K, Parekh VS, Zhang IX, Thompson B, Zhang D, Ware SA, Haataja L, Qi N, Parker SCJ, Arvan P, Yin L, Kaufman BA, Satin LS, Sussel L, Stitzel ML, Soleimanpour SA

Science. 2025 Apr 11;388(6743):eadf2034.
doi: 10.1126/science.adf2034

Brief Summary: In a series of elegant experiments in mouse models, loss of mitochondrial quality control triggered a retrograde signalling response in β-cells, hepatocytes, and brown adipocytes, impairing cellular identity and maturity.

Comment: Mitochondrial function is vital for maintaining cellular health. However, continuous exposure to environmental stressors makes mitochondria vulnerable to dysfunction. To preserve their integrity, eukaryotic cells have developed a *mitochondrial quality control (MQC) mechanism*. MQC is a crucial cellular process that ensures the proper function and health of mitochondria. It involves a complex network of mechanisms aimed at preventing the accumulation of damaged mitochondria and maintaining cellular homeostasis. Control mechanisms include mitophagy, genome maintenance, fusion/fission.

Several studies have shown that insulin-producing pancreatic β-cells of patients with T2D have abnormal mitochondria and are unable to generate energy. The current study reveals that mitochondrial dysfunctionin quality control triggers a retrograde signalling pathway that disrupts the identity and maturity of pancreatic beta cells, resulting in reduced β-cell mass not through apoptosis, but through dedifferentiation.

To determine whether impaired MCQ can lead to β-cell failure, researchers developed mouse models lacking key components of this protective machinery. One model had a disruption in mitophagy, impairing the clearance of damaged mitochondria. Another showed mitochondrial DNA depletion, resulting in reduced mitochondrial genetic content. A third model exhibited defective mitochondrial fusion, a process essential for maintaining mitochondrial integrity. Despite targeting different mechanisms, all models revealed the same outcome: a reduction in β-cell mass without detectable cell death. This striking similarity suggests a shared pathway leading to β-cell dedifferentiation or immaturity, rather than apoptosis.

When MQC is impaired, *a retrograde signalling pathway is activated* Using this pathway, the mitochondria can send signals to the nucleus and change the fate of the cell, leading to cellular dedifferentiation rather than apoptosis in response to mitochondrial damage. Mitochondrial retrograde signaling is triggered by the *Integrated Stress Response (ISR) pathway*, a cellular defense mechanism activated by mitochondrial dysfunction, oxidative stress, ER stress, nutrient deprivation, and viral infection. To test the importance of the ISR pathway in β-cell maturity, genetically engineered mice in the MQC (via mitophagy)- were treated with ISRIB, a well-established pharmacologic inhibitor of the ISR. ISRIB treatment prevented β-cell mass loss and improved glucose intolerance, suggesting its potential for the treatment or prevention of metabolic disorders

These experiments were repeated in liver cells and brown adipocytes. As in β-cells, mitochondrial quality control loss did not trigger apoptosis but instead reduced mature hepatocyte markers and increased immaturity markers. A similar stress response was activated in brown adipocytes, impairing their function. Inhibiting the retrograde mitochondrial signalling pathway can restore β-cell mass and identity, suggesting that targeting this pathway could be a promising approach for treating metabolic disorders.

Key message: Previously, it was believed that the maintenance of β-cell mass depended on a balance between β-cell replication and apoptosis. It is now recognized that β-cell dedifferentiation is a critical process contributing to β-cell dysfunction in T2D.

12.9. Steatotic liver disease in pediatric obesity and increased risk for youth-onset type 2 diabetes

Putri RR, Casswall T, Danielsson P, Marcus C, Hagman E

Diabetes Care. 2024 Dec 1;47(12):2196-2204.
doi: 10.2337/dc24-1236

Brief Summary: Using data from >10,000 children in the Swedish Childhood Obesity Treatment Register (BORIS) and >59,000 general population comparators, the authors found that metabolic dysfunction–associated steatotic liver disease (MASLD, formerly known as NAFLD) in children with obesity increases the risk of youth-onset T2D. MASLD was associated with a 2.7-fold increased risk of developing T2D, independent of other risk factors. Notably, the combination of MASLD and dysglycemia had a synergistic effect, conferring a 9-fold increased risk. Importantly, a reduction in BMI SDS through obesity treatment significantly reduced this risk in individuals who responded to treatment.

Comment: MASLD and T2D are strongly associated in adults, with each condition increasing the risk of the other; the prevalence of MASLD exceeds 70% among people with T2D, and MASLD is a major predictor for the development of T2D, with a twofold higher incidence of diabetes observed in those with MASLD. Overweight, obesity, and insulin resistance are key shared risk factors. The risk of developing diabetes rises in parallel with the severity of hepatic steatosis and fibrosis, and improvement or resolution of MASLD is associated with a reduction in diabetes risk. Both conditions are driven by insulin resistance, adipose tissue dysfunction, and chronic low-grade inflammation, which promote hepatic lipid accumulation, mitochondrial dysfunction, and hepatocellular injury. The coexistence of MASLD and T2D amplifies the risk of both liver-related and extrahepatic complications, including cardiovascular disease and malignancy.

Similarly, this study now provides compelling longitudinal data linking pediatric MASLD to a markedly higher risk of youth-onset T2D, especially when coupled with non-diabetes range dysglycemia. Because youth-onset T2Dis a generally more aggressive disease than in adults, and since MASLD is at higher risk for progression in adolescents than adults, early identification and integrated management of these metabolic perturbations and others (renal hyperfiltration, OSA, dyslipidemia, polycystic ovary syndrome etc.) should be standard practice in pediatric obesity and diabetes care to prevent full-blown metabolic decompensation.

Key Message: Routine identification and management of MASLD should be standard practice in pediatric obesity care, as it identifies children at highest risk of youth-onset T2D, other metabolic dysfunction, and long-term cardiorenal disease.

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12.10. Enhancing metabolic syndrome prediction with hybrid data balancing and counterfactuals

Shah SP, Mamun A, Soumma SB, Ghasemzadeh H

arXiv: 2504.06987 (2025) (preprint)
doi: 10.48550/arXiv.2504.06987

Brief Summary: Using machine learning models, this study addresses the challenges of accurately predicting the Metabolic syndrome (MetS). Probability analysis revealed that elevated blood glucose had the highest likelihood (85.5%), while triglycerides showed the strongest predictive power (75%).

Comment: As the global prevalence of MetS has increased exponentially over the past decade, accurate prediction remains a challenge due to data scarcity and methodological consistencies, which can affect model reliability and clinical applicability. To address these challenges, this study used advanced machine learning models to overcome these limitations.

Following data preprocessing, which included demographic, clinical, and laboratory measurements from 2,402 individuals, several approaches were applied: model selection and evaluation, oversampling strategies, class imbalance handling, and counterfactual analysis. The counterfactual analysis identified the minimal changes required to shift individuals from MetS-positive and MetS-negative classifications. Accordingly, the most frequently modified features were blood glucose (50.3%) and triglycerides (46.7%), followed by waist circumference and HDL cholesterol. Triglycerides (74.9%) and blood glucose (58.7%) also emerged as strong predictors of MetS.

The authors conclude that combining data balancing methods with counterfactual analysis can enhance the prediction of MetS. This approach has the potential to be applied in other settings, where it may perform as well as or even better than traditional methods.

Lipid Metabolism

12.11. Plozasiran, an RNA interference agent targeting APOC3, for mixed hyperlipidemia

Ballantyne C.M. *et al.*
New England Journal of Medicine 391, 899-912 (2024).
doi: 10.1056/NEJMoa2404143

Brief Summary: This double-blind, randomized trial evaluated the safety and efficacy of plozasiran, a small interfering RNA (siRNA) that reduces hepatic expression of APOC3, in adults with mixed hyperlipidemia.

Comment: Mixed hyperlipidemia is marked by elevated levels of both low-density lipoprotein (LDL) cholesterol, triglycerides and reduced levels of high-density lipoprotein (HDL) cholesterol. It affects an estimated 0.5% to 4% of the population and is associated with increased risk of developing atherosclerosis cardiovascular disease (ASCVD). 1 Triglycerides serve as a surrogate marker for atherogenic triglyceride-rich lipoproteins (TRLs), including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and chylomicron remnants. These TRLs carry up to 4-times more cholesterol per particle than LDL, contributing significantly to ASCVD risk, even in patients receiving LDL-lowering therapy. Despite its prevalence and potential health consequences, it is often underdiagnosed and undertreated.

Apolipoprotein C-III (APOC3), a glycoprotein produced primarily in the liver, is present on most major lipoproteins, including chylomicrons, VLDL, LDL, HDL, and lipoprotein(a). 2 It plays a central role in lipid metabolism by inhibiting lipoprotein lipase activity and decreasing hepatic uptake of TRLs. This leads to elevated circulating levels of triglycerides and TRLs. Conversely, APOC3 loss-of-function variants are associated with lower triglyceride levels, a 40% reduction in ASCVD risk, and increased longevity.

RNA interference (RNAi) is a natural cellular mechanism that regulates gene expression after transcription. Discovered in the late 1990s by Andrew Fire and Craig Mello, RNAi reshaped our understanding of how genes are controlled.3 Small interfering RNAs (siRNAs), typically 21–23 nucleotides long and double-stranded, are engineered to match specific mRNA sequences. Once inside the cell, siRNAs trigger the formation of RNA-induced silencing complexes (RISCs), which bind to the target mRNA and promote its degradation, thereby blocking the production of disease-related proteins.

Plozasiran is a small interfering RNA (siRNA) specifically designed to reduce hepatic expression of APOC3. Plozasiran was evaluated in 353 adults with mixed hyperlipidemia who were already on stable statin therapy. Three groups received plozasiran injections every three months (10, 25, or 50 mg), while a fourth group received 50 mg every six months. Placebo injections matched each dosing schedule for comparison. By week 24,

plozasiran significantly lowered fasting triglyceride levels in all dosing groups, albeit with some worsening of glycemic control. Importantly, these effects were sustained through week 48, 36 weeks after the final dose. Considering both efficacy and the risk of glycemic deterioration, the 25 mg quarterly dose was selected, as it provided substantial triglyceride reduction with the lowest rate (7%) of glycemic worsening.

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12.12. Lipidomic signatures linked to gut microbiota alterations in children and adolescents with type 2 diabetes mellitus and metabolic syndrome

Mora-Godínez S, de la Garza AL, Tamez-Rivera O, Senés-Guerrero C, Carrizales-Sánchez AK, García-Rivas G, Hernández-Brenes C

Sci Rep. 2025 Jun 3;15(1):19427.
doi: 10.1038/s41598-025-04343-3

Brief Summary: The authors performed an untargeted lipidomic analysis using liquid chromatography–mass spectrometry in children aged 7–16 years, comparing 10 children in each group: T2D, MetS, and healthy controls. They examined associations with obesity, metabolic risk factors, inflammatory biomarkers, and gut microbiota. Of the 375 annotated plasma lipids identified, differences compared to healthy controls were found in 45 and 47 lipid species in MetS and T2D, respectively. Several lipid species were associated with specific gut microbial taxa, suggesting a potential interplay between lipid metabolism and gut microbiome composition.

Comment: Although lipidomics has been linked to cardiometabolic risk over the past decade, few studies have focused on pediatric populations. This novel study integrated plasma lipidomic profiling with microbiome analysis in children and adolescents with T2D and MetS.

As expected, subjects from both groups showed higher body mass index (BMI), waist-to-height ratio, insulin levels, and insulin resistance (HOMA-IR). Pro-inflammatory cytokines were elevated particularly in individuals with T2D. The study identified distinct lipid profiles associated with T2DM and MetS in children and adolescents. These included increased levels of phosphocholines, phosphoinositols, and sphingomyelins, and decreased levels of ether phospholipids (ePLs) and lysophospholipids (lyso-PLs).

Phosphocholines and phosphoinositols were positively correlated with BMI, waist circumference, HOMA-IR, and pro-inflammatory cytokines; certain sphingomyelins were increased and linked to HOMA-IR suggesting they could play an important role in early signaling of metabolic dysfunction. Ceramides were positively correlated with glucose and insulin levels, making them potential markers for insulin resistance. The elevated levels of phosphocholines, phosphoinositols, sphingomyelins, triglycerides, and ceramides found in MetS and T2DM subjects reveal lipid pathways related to lipotoxicity, membrane remodeling, and disrupted phospholipid metabolism. The observed reduction in ether phospholipids, plasmalogens, and lysophospholipids may reflect impaired antioxidant defenses and dysregulated lipid metabolism, potentially due to reduced activity of enzymes such as lysophosphatidylcholine acyltransferase.

Additionally, lipid species showed correlations with specific gut microbiota. In MetS, lipids were positively correlated with gut microbes from the Enterobacteriaceae family and Pseudomonas aeruginosa, while in T2DM, correlations were observed with Enterobacteriaceae family and Enterococcus casseliflavus. These findings support the idea that there is a significant interaction between lipid metabolism and gut microbiota in metabolic diseases.

By linking lipidomic changes to both metabolic dysfunction and gut microbiota alterations, the study suggests potential avenues for therapeutic interventions, including dietary strategies and microbiome modulation, to address metabolic diseases in pediatricpopulations.

Key message: By demonstrating a link between lipidomic profiles and gut microbiota composition in MetS and T2D, this study highlights potential therapeutic avenues, such as dietary strategies and microbiome modulation, for managing metabolic diseases in children and adolescents.

12.13. Evinacumab in homozygous familial hypercholesterolaemia: long-term safety and efficacy

Gaudet D, Greber-Platzer S, Reeskamp LF, Iannuzzo G, Rosenson RS, Saheb S, Stefanutti C, Stroes E, Wiegman A, Turner T, Ali S, Banerjee P, Drewery T, McGinniss J, Waldron A, George RT, Zhao XQ, Pordy R, Zhao J, Bruckert E, Raal FJ
Eur Heart J. 2024 Jul 12;45(27):2422-2434.
doi: 10.1093/eurheartj/ehae325

Brief Summary: In this long-term, open-label Phase 3 trial of 116 individuals with homozygous familial hypercholesterolemia (HoFH), evinacumab administered every 4-weeks reduced low-density lipoprotein cholesterol (LDL-C) levelsby 43.6% overall, with greater reductions in adolescents (55.4%) than adults (41.7%).

Comment: Homozygous familial hypercholesterolemia (HoFH)is characterized by extremely elevated plasma LDL-C and accelerated atherosclerosis. Its estimated prevalence is ~1:350,000 to 1:400,000. The most common genetic cause is a variant in the LDL-receptor (LDLR) gene (85%to 90%). [1] Less frequently, variants occur in the apolipoprotein B (APOB) gene (5% to 10%), the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene (1% to 3%) or the rare autosomal recessive form caused by biallelic variant of the LDLR adaptor protein 1 (LDLRAP1). If left untreated, HoFH results in fatal and nonfatal myocardial infarctions as early as the first two decades of life. Current treatments, including diet, statins, ezetimibe, and PCSK9 inhibitors, often fail to achieve sufficient LDL-C reduction in most subjects affected by HoFH.

Angiopoietin-like protein 3 (ANGPTL3) is a hepatokine that inhibits lipoprotein lipase (LPL), an enzyme responsible for breaking down triglycerides from chylomicrons and very low-density lipoproteins (VLDL), as well as endothelial lipase (EL), which hydrolyzes HDL phospholipids and lowers HDL-C levels. Genetic deficiency in ANGPTL3 is associated with a lower risk of ASCVD and reduced plasma concentrations of LDL-cholesterol, triglyceride-rich lipoproteins (TRLs), and HDL-cholesterol. Inhibition of ANGPTL3 enhances the activity of both LPL and EL, thereby increasing lipolysis and remodeling of VLDL particles. This promotes the conversion of VLDL to intermediate-density lipoproteins (IDL), facilitates hepatic clearance of VLDL remnants and IDL particles, and ultimately reduces the production of LDL particles.

Evinacumab is a fully human monoclonal antibody that specifically binds to and inhibits ANGPTL3. It was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2021 as an adjunct to other lipid-lowering therapies for the treatment of HoFH in adult and adolescent patients aged ≥ 12 years, and in 2023 for children aged 5–11 years. The current study evaluated the long-term safety and efficacy of evinacumab over a median duration of 104 weeks (range: 28–196) in adults and adolescents with HoFH.

Evinacumab treatment for up to 4 years effectively reduced LDL-C levelsand other lipids and lipoproteins in patients with HoFH, with a safety profile that was consistent with previous studies.

An editorial accompanying the article highlighted several limitations and unresolved gaps.[2] These include the absence of a control group, follow-up data available for less than 50% of the cohort beyond two years, the small number of adolescent patients over 12 years of age, and the lack of data on children. Additionally, 80% of participants were white adults, limiting generalizability. Current guidelines recommend initiating treatment for HoFH at diagnosis, ideally by age 2; however, this study only included individuals aged 12+ years. The editorial also emphasized the need to simplify treatment by transitioning from intravenous to subcutaneous administration of evinacumab.

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12.14. Efficacy and safety of inclisiran in adolescents with genetically confirmed homozygous familial hypercholesterolemia: results from the double-blind, placebo-controlled part of the ORION-13 randomized trial

Wiegman A, Peterson AL, Hegele RA, Bruckert E, Schweizer A, Lesogor A, Wang Y, Defesche J

Circulation. 2025 Jun 24;151(25):1758-1766.
doi: 10.1161/CIRCULATIONAHA.124.073233

Brief Summary: This 1-year, double-blind, placebo-controlled phase 3 study assessed the efficacy and safety of inclisiran in adolescents (12 to $<$18 years of age) with homozygous familial hypercholesterolemia.

Comment: *RNA interference (RNAi)* is a natural biological process in which double-stranded RNA molecules mediate sequence-specific gene silencing, either by degrading messenger RNA (mRNA) or by inhibiting its translation. This mechanism plays a critical role in regulating gene expression. The discovery of RNAi, for which Andrew Fire and Craig Mello were awarded the 2006 Nobel Prize in Physiology or Medicine, was a major breakthrough in molecular biology.A key component of the RNAi pathway is small interfering RNA (siRNA), also known as short interfering RNA or silencing RNA. siRNAs are double-stranded, non-coding RNA molecules typically 20–24 base pairs in length. They guide the RNA-induced silencing complex to complementary mRNA targets, leading to mRNA degradation and, consequently, inhibition of protein translation.

Inclisiran is a small interfering RNA that targets hepatic *PCSK9* synthesis. By reducing intrahepatic *PCSK9* levels, inclisiran upregulates LDL receptors (LDLRs), thereby increasing LDL-C uptake and lowering circulating LDL-C levels, except in individuals with null variants in both *LDLR* alleles. A recent meta-analysis demonstrated that among adults, inclisiran treatment led to a pooled mean LDL-C reduction of -48.6% in individuals with heterozygous familial hypercholesterolemia (HeFH). However, the reduction was much smaller in those with homozygous FH (HoFH: -9.1%). The current study assessed inclisiran treatment in adolescents with HoFH. At day 330, the mean$\pm$SD percentage change in LDL-C from baseline was $-21.6\pm$ 13.4% in the inclisiran group, compared to an increase of $+11.7\pm30.5\%$ in the placebo group. Among adolescents receiving inclisiran, 56% (5/9) achieved an LDL-C reduction greater than 15%, 33% (3/9) had reductions over 20%, and 33% had reductions exceeding 30%. Subgroup analysis by genotype demonstrated that inclisiran lowered LDL-C consistently, regardless of the specific causal genetic variant associated with HoFH.

Inclisiran was well tolerated, with a safety profile comparable to that observed in adults. No new safety concerns emerged; there were no serious adverse events, deaths, or treatment discontinuations related to adverse effects.

The results in adolescents are consistent with those observed in adults. On one hand, there is a meaningful reduction in cholesterol levels and a significant difference compared to placebo. In addition, the convenience of treatment, administration once every six months, should not be overlooked. On the other hand, individuals with homozygous mutations are more severely affected and tend to have extremely higher LDL-C levels. Thus, even a 20% reduction may still leave their LDL-C levels well above target.

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12.15. Impact of metabolic-associated fatty liver disease on the cholesterol efflux capacity of high-density lipoproteins in adolescents with type 2 diabetes

Orozco Morales JA, Medina Urrutia AX, Tamayo MT, Reyes Barrera J, Galarza EJ, Juárez Rojas JG, Dies Suarez P, Méndez Sánchez N, Díaz Orozco LE, Velázquez-López L, Medina Bravo P

Front Pediatr. 2024 Dec 24;12:1462406.
doi: 10.3389/fped.2024.1462406

Brief Summary: This cross-sectional study, in adolescents with T2D, found that metabolic-associated fatty liver disease (MAFLD) does not impair HDL's cholesterol efflux capacity (CEC). However, MAFLD is associated with alterations in HDL structure and lipid content, which could affect HDL long-term protective role against cardiovascular disease.

Comment: High-density lipoproteins (HDLs) havea known protective role against cardiovascular disease (CVD). While low plasma HDL cholesterol (HDL-C) levels are an independent risk factor for CVD, recent evidence suggests that HDL functionality and physicochemical properties may provide a more accurate reflection of cardiovascular risk than HDL-C concentration alone.HDLs exert their protective effects through several mechanisms. One key process recognized is *reverse cholesterol transport (RCT),*in which HDL shuttles cholesterol from peripheral tissues back to the liver for biliary excretion. Another crucial process isthe *cholesterol efflux capacity (CEC)*, referring to HDL's ability to remove cholesterol from macrophages. Higher CEC is associated with a lower CVD. risk.

T2D is associated with metabolic-associated fatty liver disease (MAFLD). Previous studies have reported a reduced in CEC in adults with MAFLD. The aim of this study was to assess the impact of MAFLD on CEC in adolescents with T2D.

The study cohort comprised of three groups: adolescents with T2D without MAFLD group ($n = 16$), T2D with MAFLD ($n = 31$) and health controls ($n = 23$). Surprisingly, no differences in HDL CEC were found between adolescents with T2D with and without MAFLD, nor between adolescents with T2D and healthy controls. However, in adolescents with T2D, higher liver fat content was associated with notable changes in HDL characteristics: lower levels of larger HDL2 particles, a shift towards smaller HDL3 particles, increased triglyceride content inside HDL, and reduced cholesterol esters and free cholesterol within HDL particles. These alterations suggest early

Key message: in adolescents with T2D, hepatic lipid accumulation drives changes in HDL function, increasing cardiovascular risk over time.

12.16. Living happily ever after? the hidden health risks of Disney princesses

van Dijk SHB, Bui M, Eijkelboom AH
BMJ. 2024 Dec 16;387:q2497.
doi: 10.1136/bmj.q2497

Brief Summary: This article examines the health profiles of Disney princesses and assesses *do they truly "live happily ever after"*? It offers a unique perspective on the long-term health implications of their portrayed lifestyles.

Comment: Published in the Christmas edition of the *BMJ,* this article critically reviews the potential health risks associated with the lifestyles of Disney princesses. For example, Snow White's prolonged social isolation—a recognized risk factor for cardiovascular disease, depression, and all-cause mortality—raises concerns about her long-term well-being. Aurora, or Sleeping Beauty, faces a different threat: the health risks of excessive sleep. Prolonged sleep duration has been linked to cardiovascular disease, stroke, obesity, and T2D. Don't miss the discussion on the potential comorbidities affecting the other princesses.

13. Global Health for the Paediatric Endocrinologist

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Introduction

This year's Global Health chapter includes articles on disease prevention with expansion and improvement in newborn screening, implications of undernutrition and the simultaneous rise in rates of obesity, the use of insulin analogs in resource constrained setting and predictions for global rates of type 1 diabetes. Understanding the variations in disease incidence and treatment practices, determining the feasibility of utilizing newer therapies and working to establish methods for improving and tracking care delivery will improve our ability to meet the needs and improve the health of those living in low and middle-income countries affected by endocrine disorders.

Endocrinology

13.1. Early childhood height, weight, and BMI development in children with monogenic obesity: a European multicentre, retrospective, observational study

Zorn S, de Groot CJ, Brandt-Heunemann S, von Schnurbein J, Abawi O, Bounds R, Ruck L, Guijo B, Martos-Moreno GÁ, Nicaise C, Courbage S, Klehr-Martinelli M, Siebert R, Dubern B, Poitou C, Clément K, Argente J, Kühnen P, Farooqi IS, Wabitsch M, van den Akker E

Lancet Child Adolesc Health. 2025 May;9(5):297-305.

PMID: 40246357 doi: 10.1016/S2352-4642(25)00065-3.

Erratum in: Lancet Child Adolesc Health. 2025;9(6):e14.

doi: 10.1016/S2352-4642(25)00128-2.

Brief Summary: This European multi-center study analyzed early childhood growth trajectories in 147 children with genetically confirmed monogenic obesity. Distinct genotype-specific patterns of BMI development were identified. The authors propose a BMI cutoff ≥ 24.0 kg/m^2 or ≥ 4.69 SDS at age 2 years as a clinical threshold to distinguish children with biallelic *LEP*, *LEPR*, and *MC4R* variants from those with common obesity or monoallelic variants.

Monogenic obesity is a rare cause of obesity involving single gene mutations in the leptin–melanocortin pathway, which is crucial for regulating appetite and energy expenditure. It typically presents with severe, early-onset obesity and hyperphagia. Early diagnosis is critical to enable targeted pharmacological interventions, such as MC4R agonists or leptin analogues. However, access to genetic testing remains uneven across countries, and distinguishing monogenic from common obesity is often challenging due to overlapping phenotypes. This study addresses a key gap by proposing data-driven BMI thresholds for early genetic screening, based on the largest pooled cohort of monogenic obesity cases to date.

The authors highlight the value of early growth trajectories in selecting candidates for genetic testing. The steep BMI rise during the first year of life, followed by a plateau in biallelic *LEP*, *LEPR*, and *MC4R* variants - distinct from the rapid (yet less steep) and persistent BMI increase in *POMC* cases - can guide early recognition. Accelerated linear growth in biallelic MC4R carriers offers an additional diagnostic clue. Monoallelic *MC4R* variant carriers show a gradual BMI rise, undistinguishable from common obesity.

The proposed BMI thresholds, especially when combined with features such as hyperphagia or rapid linear growth, provide a practical tool to guide early identification of individuals with suspected monogenic obesity and a foundation for future genetic screening guidelines. Further validation in diverse populations and integration of additional genes linked to monogenic obesity will be essential to refine diagnostic algorithms and promote equitable access to personalized therapies in pediatric obesity care.

13.2. Improved food habits and anthropometry among primary school children following a novel healthy eating programme

Seneviratne SN, Sachchithananthan S, Angulugaha Gamage PS, Peiris R, Wickramasinghe VP, Somasundaram N
Pediatr Obes. 2025 Apr;20(4):e13171.
PMID: 39228329 doi: 10.1111/ijpo.13171

Brief Summary: This non-controlled intervention study evaluated the effects of a school-based healthy eating program in Sri Lanka on food habits and body mass index (BMI) assessed 9 months after intervention. It found sustained positive effects suggesting theintervention as a useful tool to improve nutritional status in low and middle-income countries (LMICs).

Sri Lanka faces the dual problem of a rise in overnutrition with a continued significant incidence of undernutrition. To combat these issues, the authors developed a 3-week school-based intervention to improve knowledge and encourage healthier eating habits among primary school children. This included an age-appropriate motivational storybook illustrating the benefits of a healthy diet and adverse effects of an unhealthy lifestyle and a picture/sticker-based food diary. The program was implemented in 2018-2019 among >1000 grade 1-2 students in 4 state schools in Columbo, Sri Lanka. The study assessed changes in eating habits and change in BMI z-score from baseline after 9 months.

Of the initial 1042 participants, 868 completed the follow-up (83%). Most children had normal BMI at baseline (69%), 17% were underweight, 8% overweight and 6% obese. At follow-up, children who were initially underweight or normal weight showed increases in mean BMI z-score (UW: -2.8 to -2.2, $P<0.001$ and NW: -0.7 to -0.6, $P<0.001$), while those who were overweight and obese showed no change in BMI z-score (OW: $+1.5$ to $+1.49$, $P=0.83$ and OB: $+2.85$ to $+2.21$, $P=0.19$). Children with underweight showed a healthy increase toward the median and those with overweight and obesity did not continue to increase. Eating habits were assessed by a one-week food diary and food diary score (FD). Mean FD score 65%at follow-up indicated an improvement of 16.5% in food habits from the baseline score of 51% +/- 23% ($P<0.001$)

The authors postulate that the success of the program was partly due to the child-friendly, self-motivational and interactive nature of the program with some degree of activity-based parental involvement. While acknowledging the lack of a control group, this short-term educational intervention shows promise for improving nutritional status in young children in LMICs.

13.3. Risks and benefits of weight gain in children with undernutrition

Strassmann BI, Vincenz C, Villamor E, Lovett JL, Dolo ZD, Shedden K
JAMA Netw Open. 2025 Jun 2;8(6):e2514289.
PMID: 40478571 doi: 10.1001/jamanetworkopen.2025.14289

Brief Summary: This prospective cohort study in Mali evaluated the potential risks and benefits of weight gain in children with undernutrition. A 1 SD increase in weight between ages 1 to 10 years was associated with taller stature, but not with an increased risk of obesity or hypertension.

In low- and middle-income countries (LMICs), concern has been raised about the influence of rapid relative weight gain in children over 2 years of age on development of obesity and/or hypertension in adulthood. However, persistent undernutrition can affect longitudinal growth and adult height as well as result in increased

morbidity and mortality. The authors analysed data from the Dogon Longitudinal Study, a 21-year population-based multigenerational cohort study conducted in Mali from 1998 to 2019. This cohort included 1348 individuals aged 5 years or younger in April 1998 and all children born after that date until July 2000 with multiple measurements of weight, height and systolic blood pressure (SBP).

Using mediation analysis, the authors quantified the direct and indirect associations between childhood weight and adult SBP at 21 years of age. Adjustments were made for the height and SBP of both parents to reduce genetic confounding. Children who showed a 1SD weight increase over the first decade of childhood were taller: mean height increased by 3.0 cm in girls and 4.1 cm in boys. They also had higher BMI and SBP at 21 years, but none of these children became obese and few became hypertensive in adulthood.

This study illustrates the potential advantages of improved weight gain to increase longitudinal growth in this setting, and the need for public health policy in LMICs to improve childhood nutrition.

13.4. Barriers to the management of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency

Eitel KB, Fechner PY

J Clin Endocrinol Metab. 2025 Jan 21;110 (Supplement_1):S67-S73.
PMID: 39836619. doi: 10.1210/clinem/dgae710

Brief Summary: This article reviews the barriers to care among patients with congenital adrenal hyperplasia (CAH). It highlights key issues, such as the importance of universal newborn screening, the consequences of inadequate care, and the sociocultural and financial obstacles that families face when managing the disease.

Newborn screening (NBS) for CAH improves outcomes by allowing early diagnosis and prevention of life-threatening crises. However, while NBS is widely implemented in developed nations, it is absent or limited in many parts of the world. Even in countries with high uptake of NBS, gaps in care remain due to regional disparities and logistical issues, such as delays in obtaining test results or limited access to follow-up care.

Following diagnosis, families in rural or remote areasface difficulties accessing specialist care. Financial barriers further complicate access to medications and specialists. In many cases, medication access can be inconsistent, and families may lack the knowledge or resources to administer medications properly, particularly stress dosing. Financial constraints often prevent families from accessing care, medications, or necessary diagnostic tests. Insurance challenges and out-of-pocket costs contribute to delays in treatment or adherence to prescribed regimens.

Stigmatization, especially regarding genital ambiguity, can lead to avoidance of medical care, concealment of the condition, or social isolation. This is particularly true in cultures where gender roles are strictly defined, and where treatment decisions may be influenced by societal expectations. Many individuals with CAH, particularly women, face traumatic experiences in medical settings and these experiences contribute to avoidance of medical care in adulthood.

The authors emphasize the need for improved resources and support for those with CAH. This includes more widespread implementation of NBS programs and improved access to comprehensive care centers with appropriate multidisciplinary teams for management. They also emphasize the importance of support networks for those with CAH, particularly in rural or isolated areas, including options for telehealth and online support. Continued efforts are needed to decrease patient and family burden and improve quality of life for those with CAH.

13.5. High carrier frequency of CYP21A2 gene mutations in southern india - underscoring the need for genetic testing in congenital adrenal hyperplasia

Ravichandran L, Paul S, Rekha A, Asha HS, Mathai S, Simon A, Danda S, Thomas N, Chapla A

Endocrine. 2024 Jul;85(1):363-369.
PMID: 38441846 doi: 10.1007/s12020-024-03747-x

Brief Summary: This genetic screening study in South India evaluated the carrier frequency of *CYP21A2* mutations in a population with high incidence of CAH and high rate of consanguinity. The authors advocate for genetic screening in those at high risk due to a family history of CAH, history of consanguinity, or history of early infant death.

Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency is more common in India than many other countries. While newborn screening allows for identification of cases, it has limitations. Given the high incidence of CAH in India and a rate of consanguineous marriage as high as 30%, the authors screened 1034 healthy individuals with no known relevant history to identify the carrier frequency of hotspot mutations in *CYP21A2*in the South Indian population.

Blood samples were obtained from 1034 asymptomatic individuals (432 males and 602 females) collected as control samples for other projects. Genotyping was performed for 9 common mutations in *CYP21Q2* (30kb deletion. P30L, I2G, 8 bp del, 1172N, E6CLUS (I235N, V236E, M238K), V281L, Q318X and R356W). Genotypingidentified 101 carriers (39 males and 62 females) giving a carrier frequency of 9.76%. The most common mutation was the 30kb deletion (4.6%) with chimera I(CHI) in 18 cases.

While the carrier frequency in the South India population is similar to that previously reported in Europe, there is a high frequency of classical mutations compared to non-classical mutations (8.64% vs 1.07%). This suggests that some subgroups may be at high risk of developing classical CAH. The authors calculate that the identified heterozygous carrier frequency would result in an estimated prevalence of classical CAH of 1 in 416. This is 5 times higher than the reported incidence based on South Indian newborn screening data reported by the Indian Council of Medical Research (1 in 2036). This disparity may be attributed to a higher neonatal mortality among the unscreened newborns or to other unknown factors.

The authors advocate for CAH carrier screening programs among those with a family history of CAH, a family history of consanguinity, partners of CAH affected individuals, and couples with a history of infant death to allow appropriate decision-making and early intervention if indicated.

13.6. Prevalence and predictors of short stature in children aged 3-18 years in Hainan Province, China: a cross-sectional study

Yan M, Qin Y, Li H, Huang C, Li H, Liu L, Cai Y, Fan L, Xiang W, Huang X
Front Pediatr. 2025 Jan 20;13:1522060.
PMID: 39902060 doi: 10.3389/fped.2025.1522060

Brief Summary: This cross-sectional study evaluated the prevalence of short stature in a clustered random sample of children in Hainan Province, China, and the factors associated with short stature in this population. Short stature was associated withlower birth weight, lower childhood body mass index z-score, lower maternal education, lower family income and lower protein intake.

Previous studies in China reported an average prevalence of short stature of 2.4% (defined by WHO Z-score $<$-2 SD) with some variation according to the specific population. Height is multifactorial, influenced by genetic, environmental, nutritional, social and other factors. To investigate the impact of non-genetic factors on short stature in children in Hainan Province, the authors conducted this large cross-sectional survey of children between the ages of 3 and 18 years through a staged, cluster random sampling method. The authors used a parent questionnaire that included height, weight, gender, birth weight, paternal/maternal education, family income, weekly intake frequencies of fruits, beans, meat and eggs, weekly intake frequencies of a variety of snacks, daily outdoor activity and daily electronic screen times.

Demographic and dietary questionnaires and measured height and weight in 26,189 children aged 3-18 years were analyzed. The prevalence of short stature ($<$-2SD) was 2.9% in boys and 3.1% in girls. Those with short stature had lower parental education and annual family income than other children, and less frequent intakes of beans, meat, eggs and fruit. Short stature children also had more low birth weight, gestational age $<$ 37 weeks and low current weight. The prevalence of short stature among rural children was more than twice that in urban children (3.76% vs 1.71%).

Hainan Province lags behind other provinces in China in economic development and this study shows a higher prevalence of short stature in this province compared to the larger Chinese population (2.4%). This may be the result of socioeconomic and nutritional factors, as well as pregnancy related issues. Attention to these issues may result in improved growth and stature in this area of China.

13.7. Physical late effects of treatment among survivors of childhood cancer in low- and middle-income countries: a systematic review

Wong KA, Moskalewicz A, Nathan PC, Gupta S, Denburg A
J Cancer Surviv. 2025 Jun;19(3):1-17.
PMID: 38183576 doi: 10.1007/s11764-023-01517-8

Brief Summary: This systematic review summarises literatureon the late effects of treatment for childhood cancer in low- and middle-income countries (LMICs). The authors found substantial knowledge gaps with no low-income country data and variable assessment of late effects in middle-income countries indicating the need for more systematic data collection.

With large populations of younger people, LMICs now account for the majority of global cancer burden. Although cure rates are lower than in high-income countries (HICs), many children do survive. To examine the physical late effects in cancer survivors in LMICs, the authors reviewed the literature to examine data available for those more than 5 years after their initial cancer diagnosis. They found 16 articles and 5 conference abstracts, although all were from lower-middle or upper-middle income countries, and nearly half were from India.

The authors review the late effect outcomes in several organ systems. Regarding Endocrine and Reproductive systems, 13 studies examined the late effects on endocrine systems and 11 studies on the reproductive system. Growth hormone deficiency was reported in 45% of survivors in 1 study and 2 other studies reported growth hormone replacement in 2-7% of survivors. Hypothyroidism, obesity, metabolic syndrome, diabetes and dyslipidemia had highly variable prevalence. Obesity (1-46%) and metabolic syndrome (4-17%) were the most prevalent endocrine late effects. Gonadal dysfunction ranged from 3 to 47%. The quality of studies reviewed was generally moderate and most of the literature in LMICs was descriptive in nature, making it difficult to determine if there are variations from one population to another.

Studies of late effects in HICs are unlikely to be generalizable to LMIC's due to disparities in survival rates, intensity of treatment received and supportive care. Even findings from MICs may be less generalizable to LICs due to weaker health systems and poor access to diagnostic testing. Overall, while childhood cancer survivors in LMICs are at risk for late effects of treatment, there are substantial knowledge gaps that would be aided by systematic collection of data from survivor cohorts to reduce morbidity and improve quality of life.

Newborn Screening

13.8. International newborn screening: where are we in Saudi Arabia?

Alhusseini N, Almuhanna Y, Alabduljabbar L, Alamri S, Altayeb M, Askar G, Alsaadoun N, Ateq K, AlEissa MM
J Epidemiol Glob Health. 2024 Sep;14(3):638-644.
PMID: 38922570 doi: 10.1007/s44197-024-00263-z

Brief Summary: This article reviews the Newborn Screening (NBS) guidelines in Saudi Arabia, the United States, Japan, Singapore, Canada, Australia, and the United Kingdom including current recommendations, issues of economic and technical feasibility, ethical considerations and recommendations for future policy.

For those countries with NBS programs, decisions concerning which disorders to screen are based on the epidemiological, financial, and economic resources of that country. As a result, variations exist between

programs including national vs. regional/state based, the number and types of disorders screened and the screening methods. There are also variations with respect to mandatory testing vs opt in/opt out programs influenced by issues of autonomy, consent and privacy.

The cost per newborn can vary widely depending on the number of diseases screened, the types of technologies used, and the overall healthcare infrastructure of a country. The availability of tandem mass spectrometry has expanded the capacity of screening programs by allowing the detection of multiple conditions from a single blood spot. However, this is not always economically feasible. The use of next-generation sequencing has great potential, but high costs, raising concerns about the affordability and sustainability of widespread implementation. The Incremental Cost-Effectiveness Ratio (ICER) is a useful metric to assess the value of these programs. If the cost of screening is too high compared to the health outcomes, such as Quality-Adjusted Life Years (QALY), the program may not be deemed cost-effective.

Saudi Arabia adopted a nation-wide newborn screening program in 2005 and currently includes 18 disorders and will shortly add hemoglobinopathies. The authors advocate for conducting further population-based studies to assess the epidemiological data in Saudi Arabia in relation to the disease burden on the country's economy. These are essential, particularly due to the high rate of consanguinity within the population and consequently higher prevalence of genetic diseases.

As global health shifts toward value-based healthcare, countries will need to balance the sustainability of screening programs with the benefits they provide. Cost-effectiveness, ethical considerations, and public health priorities will be crucial factors in this balancing act.

13.9. Newborn screening for congenital hypothyroidism: worldwide coverage 50 years after its start

Arrigoni M, Zwaveling-Soonawala N, LaFranchi SH, van Trotsenburg ASP, Mooij CF
Eur Thyroid J. 2025 Jan 31;14(1):e240327.
PMID: 39812367 doi: 10.1530/ETJ-24-0327

Brief Summary: This article reviews worldwide implementation of Newborn Screening (NBS) for congenital hypothyroidism (CH), 50 years since the first pilot study in Canada in 1974. With a focus on the last decade, the authors detail current screening methods and coverage rates worldwide.

Undiagnosed congenital hypothyroidism (CH) can cause irreversible brain damage and early diagnosis and treatment can improve outcomes. NBS for CH allows early detection to facilitate early treatment. The first pilot program for CH newborn screening was started in 1974 in Quebec, Canada. However, in 2014, after 40 years, only 29.3% of newborns worldwide underwent NBS for CH, implying that 70.7% of newborns with CH are not detected and treated early. In this review, the authors identify countries with NBS programs added in the last 10 years, evaluate changes in coverage rates and identify which screening methods are used.

Of the 193 countries in the United Nations, the authors found 101 countries with established NBS programs, although 6 are covered by NBS programs in neighboring countries. Compared to 2014, 13 countries reported data showing implementation of an NBS program, with 9 of these in Central or Western Asia. An estimated 29.6% of the world's birth population is screened for CH. This means that 70.4% of worldwide newborns are not screened for CH. There has been only minimal increase in overall screening despite addition of new programs in the last 10 years.

The authors provide an excellent world map of areas with NBS and the coverage rate, as well as one with changes compared to 2014. While coverage has improved in many countries, there were declines in Russia and Mexico and limited or no coverage in Nicaragua, India, Albania and Moldova. In Africa, only Egypt and South Africa have structured programs, although pilot programs have started in several other countries. TSH based testing is used in ~86% of programs, which is effective for detecting primary CH, but may miss central CH.

Barriers to NBS include economic constraints, lack of political or institutional support, geographic issues, lack of personnel or laboratory capacity and cultural factors. These are particular challenges in Africa and parts of Asia where the annual birth rate is high, contributing significantly to the lack of change in worldwide coverage. Improving global NBS coverage will require attention from national governments and the international global health community.

13.10. Lessons of screening two million newborns for congenital adrenal hyperplasia: 10-year experience of the minas gerais public health program

Botelho Barra C, Souza Sena G, Pereira Oliveira H, de Paula Gonzaga ALAC, Ferreira Araújo R, Ramos Villela T, Machado Mantovani R, Nélio Januário J, Novato Silva I

J Pediatr (Rio J). 2025 May-Jun;101(3):341-348.
PMID: 39933694 doi: 10.1016/j.jped.2024.10.012

Brief Summary: This study presents a descriptive and retrospective evaluation of the Newborn Screening (NBS) program for congenital adrenal hyperplasia (CAH) in Minas Gerais state, Brazil, over a 10-year period. It reviews the system's implementation, issues with false-positive results and regional disparities.

The Minas Gerais State NBS program for 21-OH deficient CAH started in 2013. Results up to 2023 show an incidence consistent with that estimated in Brazil as a whole. Specimens are collected at days 3-5 after birth, generally at pediatric visits with coverage of 90% of births. The program uses a single-tier screening strategy with combined gestational age and birth weight-adjusted 17OHP thresholds. This approach has been effective in reducing false positives without needing expensive second-tier tests like LC-MS/MS. The program's positive predictive value increased from 2.1% in 2013 to 10.5% by 2023, largely due to changes in assay specificity and alterations in cut-off values.

Despite their highly effective program, the Minas Gerais State NBS program faces logistical challenges due to the state's large geographic size. 85% of salt-wasting cases were diagnosed via NBS after 14 days, with consequent delays in treatment and increased risks. However, no deaths were recorded due to late diagnosis. Babies diagnosed with CAH are referred to a multi-disciplinary program including pediatric endocrinologists, psychologists, and geneticists. The COVID-19 pandemic pushed the program to expand telemedicine services for consultations and management of false-positive referrals. This has shown promising results in terms of reducing unnecessary in-person visits, particularly for families in remote areas.

There are significant regional disparities in Brazil despite a national mandate since 2013, with programs in the South and Southeast regions being more efficient than in other areas. The private healthcare system has also contributes to inequities in access to follow-up care for children diagnosed through NBS. Coordination between the public and private healthcare sectors would likely improve these disparities.

The program's experience offers important lessons for other regions in Latin America and globally, particularly in addressing equity, improving screening protocols, and enhancing long-term follow-up.

Diabetes and Diabetes Technology

13.11. Treatment regimens and glycaemic outcomes in more than 100 000 children with type 1 diabetes (2013-22): a longitudinal analysis of data from paediatric diabetes registries

Zimmermann AT, Lanzinger S, Kummernes SJ, Lund-Blix NA, Holl RW, Fröhlich-Reiterer E, Maahs DM, Ebekozien O, Rompicherla S, Warner JT, Pons Perez S, Robinson H, Craig ME, Johnson S, Akesson K, Thorén A, Eeg-Olofsson K, Ranjan AG, Madsen M, Witsch M, Bratke H, Alonso GT, Sumnik Z, Neuman V, Cinek O, Skrivarhaug T, Svensson J

Lancet Diabetes Endocrinol. 2025 Jan;13(1):47-56.
PMID: 39622257 doi: 10.1016/S2213-8587(24)00279-1
Erratum in: Lancet Diabetes Endocrinol. 2025;13(4):e7.
doi: 10.1016/S2213-8587(25)00032-4

Brief Summary: This large longitudinal study analyzed data on ~140,000 children (aged ≤18 years) with type 1 diabetes (T1D) across 8 national registries from the US, Australian, Europe and Great Britain and the SWEET initiative between 2013 and 2022. Glycaemic control improved significantly - mean HbA1c reduced from 8.2% to 7.6%, the proportion of children achieving target HbA1c <7% increased, while the proportion of children with HbA1c >9%, as well as rates of severe hypoglycaemia and diabetic ketoacidosis, decreased. These

achievements coincided with marked increases in the use of diabetes technologies, such as continuous glucose monitoring (CGM) and insulin pumps (CSII).

This multinational study provides comprehensive real-world evidence of improved glycaemic outcomes and reduced acute metabolic complications among children with T1D over the past decade, advances largely driven by the growing adoption of diabetes technologies such as CGM and CSII, as well as the establishment of diabetes registries and the introduction of more stringent HbA1c targets. These findings underscore not only the clinical benefits of technology but also a broader evolution in paediatric diabetes care toward real-time, data-informed management.

However, despite this progress, a substantial proportion of children fail to meet ISPAD glycaemic targets, highlighting persistent challenges, including disparities in healthcare infrastructure and access to technology. The findings highlight the need for continued innovation, such as wider adoption of automated insulin delivery systems, and stronger support systems to help families and clinicians optimize care. Ultimately, this study reinforces the importance of sustained investment in diabetes technologies and the imperative to ensure equitable access worldwide, so that all children with T1D can benefit from modern advances in care. A significant limitation is the lack of registry data from low- and middle-income countries.

13.12. Marked improvement in HbA1c following introduction of biosimilar insulin to treatment regimen of children and youth with type 1 diabetes in Mali: a randomised controlled trial

Besançon S, Haynes A, Togo AD, Sandy JL, Maniam J, Sidibe AT, Djéneba S, de Beaufort C, Perolini MC, Gastaldi G, Beran D, Eigenmann C, Ogle GD

Diabet Med. 2025 May;42(5):e70007.
PMID: 40033680 doi: 10.1111/dme.70007

Brief Summary: This randomized controlled trial evaluated the impact of insulin analogues vs. human insulin on HbA1c in children with type 1 diabetes (T1D) in Mali. It found improvements with the use of insulin analogues. As evidence of outcomes in the use of insulin analogues in low-resource settings is lacking, this study shows promising results.

This was a 2-group parallel arm, randomized trial in 260 children with T1D diagnosed >12 months prior and naïve to insulin analogues. Subjects were randomized 1:1 to continued use of human insulin or to change to analogue insulin with a basal-bolus regimen. Insulin regimens included either Humulin NPH and R or pre-mixed insulin (70/30 NPH/R). The primary outcome was HbA1c measured at baseline and every 3 months for 1 year.

All participants received a 1-day educational program that included instruction on timing of insulin injections and blood glucose monitoring, simplified carbohydrate counting, insulin dose adjustments and hypoglycemia/hyperglycemia. Each group also received education tailored to their randomized insulin regimen. Both human insulin and insulin analogues were provided through the Life for a Child program in coordination with the Malian Ministry of Health.

From baseline to 12 months, there was a~30% relative reduction in HbA1c (from 11.6% to 8.1%) in the intervention group compared to only ~6% (from 11.4% to 10.7%) in the control group. The proportion of participants with HbA1c >14% was 38.5% at baseline and decreased to 0% at 12 months, and 41.5% had HbA1c $<$ 7.5%. Episodes of DKA declined in the intervention group (29.2% to 1.5% over 12 months) with no change in the control group. There was no change in episodes of severe hypoglycemia. A satisfaction survey showed 96.2% of the intervention group were either very satisfied or satisfied, and the remaining 3.8% undecided on the regimen.

This study shows the effectiveness and feasibility of using insulin analogues in a low-resource setting. If these improvements in glycemic control can be sustained, it would result in a substantial reduction in long-term diabetes complications. However, due to the high costs of analogue insulins, human insulin remains the mainstay in LMIC's and a switch to insulin analogues will require national and global efforts to reduce these costs.

13.13. Human vs analogue insulin for youth with type 1 diabetes in low-resource settings (human-1): protocol for a randomised controlled trial

Foulds A, Josey C, Kehlenbrink S, Rollman BL, Chang CH, Lalama C, Ansbro É, Prust ML, Zabeen B, Ramaiya K, Ogle G, Chae SR, Luo J

BMJ Open. 2025 Jan 30;15(1):e092432.

PMID: 39890140 doi: 10.1136/bmjopen-2024-092432

Brief Summary: The HumAn-1 randomized control trial aims to test if insulin glargine, a long-acting insulin analogue, reduces the risk of serious hypoglycemia and/or improves glycemic time-in-range (TIR) vs human insulin regimens. This article outlines the plans for the trial enrolling patients with type 1 diabetes from both Bangladesh and Tanzania. It uniquely uses blinded continuous glucose monitor (CGM) data to evaluate time in range and time in hypoglycemia.

The HumAn-1 trial is a 1:1 randomized, parallel-group clinical trial comparing biosimilar insulin glargine with human insulin (NPH or premixed 70/30 insulin) in 400 youth with type 1 diabetes (T1D) recruiting in Dhaka, Bangladesh ($n = 250$) and Mwanza, Tanzania ($n = 150$). All subjects will have been diagnosed >12 months prior to the study, be aged 7 to 25 years and naïve to both insulin analogues and CGM use. The control group will continue their prior therapy, either NPH with regular or pre-mixed 70/30 (NPH/R). The intervention group will receive insulin glargine. Both groups will enter a 2-week dose titration phase and will receive the same intensity of education and counseling, as well as access to supplies for the same frequency of blood glucose testing. Blinded CGM sensors will be place on both groups 5 times (14 days each) over the 12 months of study.

While the primary outcomes are percent time-in-serious-hypoglycemia (< 54 mg/dl) and percent time-in-range (70–180 mg/dl), they also plan several sub-studies including examination of Quality of Life, healthcare costs and cost effectiveness.

This study has an innovative design with the use of study sites in both South Asia and East Africa to provide geographically and culturally diverse perspectives, use of blinded continuous glucose monitoring and integrating both qualitative and quantitative measures and should provide rich data to examine the use of insulin analogues in low-resource settings.

13.14. Pediatric type 1 diabetes care in Indonesia: a review of current challenges and practice

Fauzi M, Fadiana G, Nadira D, Angela A, Puteri HA, Pulungan A

J Clin Res Pediatr Endocrinol. 2024 Nov 27.

PMID: 39601260 doi: 10.4274/jcrpe.galenos.2024.2024-9-4

Brief Summary: This article presents the current state of care for children with Type 1 diabetes (T1D) in Indonesia and the challenges faced in the country. These include a limited number of pediatric endocrinologists with uneven geographical distribution, limited access to insulin and blood glucose monitoring and difficulties with family education and support.

According to the Changing Diabetes in Children (CDiC) Indonesia database, in January 2024, there were 1210 children and adolescents living with T1D, mostly on the island of Java. This number is thought to be lower than actual, due to low reporting and poor ascertainment in rural areas beyond Java Island. The perception of a low prevalence of T1D contributes to the poor awareness of T1D among the general public as well as health care professionals in Indonesia. In 2024, the Indonesian Pediatric Society reported 39 pediatric endocrinologists with an unequal geographical distribution. As pediatric endocrinologists are the primary source of healthcare for those with T1D and its incidence appears to be rising in Indonesia, the insufficient number and unevendistribution is both a current issue and one that is likely to become more more marked without increases in workforce.

The main health insurance available to Indonesian citizens is Jaminan Kesehatan Nasional (JKN). Through this system, those with T1D receive a monthly supply of basal and prandial insulin based on the indicated doses, and 90 pieces of needle and alcohol swabs. However, the supply of insulin is sometimes insufficient, necessitating

out of pocket payments. Insulin pump therapy is used by an estimated 2% of those with T1D, due to national health insurance restrictions. Blood glucose self-monitoring is largely by finger-stick testing, but glucometers and glucose test strips are not covered by insurance and the costs are prohibitive for many families, resulting in insufficient monitoring and therefore poor glycemic control. Continuous glucose monitors are uncommon due to restrictions on coverage.

The landscape of T1D care in Indonesia reveals issues of both insufficient manpower and access to the tools necessary for appropriate glycemic control. Resolving these issues will require improvements in healthcare infrastructure and access but also comprehensive education and support for patients and families.

13.15. Estimating the total incidence of type 1 diabetes in children and adolescents aged 0-19 years from 1990 to 2050: a global simulation-based analysis

Ward ZJ, Yeh JM, Reddy CL, Gomber A, Ross C, Rittiphairoj T, Manne-Goehler J, Abdalla AT, Abdullah MA, Ahmed A, Ankotche A, Azad K, Bahendeka S, Baldé N, Jain SM, Kalobu JC, Karekezi C, Kol H, Prasannakumar KM, Leik SK, Mbanya JC, Mbaye MN, Niang B, Paturi VR, Raghupathy P, Ramaiya K, Sethi B, Zabeen B, Atun R

Lancet Diabetes Endocrinol. 2022 Dec;10(12):848-858.
PMID: 36372070 doi: 10.1016/S2213-8587(22)00276-5

Brief Summary: This study used a microsimulation model to estimate both the total and diagnosed incidence of type 1 diabetes (T1D) globally and to project childhood T1D incidence indicators from 1990 to 2050, accounting for variability in underlying incidence and health system performance of different countries.

Previous studies of T1D in children have shown large variations in incidence around the world. As this may be due to variations within health systems and issues of underdiagnosis, the authors developed a model to estimate the total and diagnosed incidence of T1D and create future projections for each country. They created a structured model that accounts for trends in health care systems and how this may impact diagnosis of T1D and its mortality. This allows assessment of whether an observed increase in T1D incidence is simply due to increased detection or represents a real increase in underlying incidence. The model takes into account a variety of other factors, synthesizing demographic, epidemiological and clinical data from multiple sources, as well as country specific genetic and environmental factors that may affect T1D incidence.

The model estimated that in 2021 there were 355,900 total new cases of T1D globally among those aged 0-19 years. However, an estimated 56% of these new cases were likely undiagnosed and therefore did not receive care for this lethal disease. Underdiagnosis varies substantially by region with over 95% of new cases correctly diagnosed in western and northern Europe, North America, Australia and New Zealand, but decreasing to 35% in west Africa, south and southeast Asia and Melanesia. Lack of diagnosis is likely due a combination of poor access to care, lack of recognition of sign and symptoms of diabetes and attribution of death to other causes. By 2050, Africa is projected to account for 51% of global new T1D cases per year, with 28% of cases projected to occur in low-income countries and 44% in lower-middle income countries where diagnosis is lowest, implying substantial risks for morbidity and mortality.

The authors point out that efforts to accelerate improvements in diagnosis of T1D will be important as there is a projected increase in total new cases due to both population growth and increase in underlying T1D rates, particularly in Africa.

Innovations in Global Health Care and Education

13.16. Telemedicine and pediatric care in rural and remote areas of middle-and-low-income countries: narrative review

Alnasser Y, Proaño A, Loock C, Chuo J, Gilman RH

J Epidemiol Glob Health. 2024 Sep;14(3):779-786.
PMID: 38478166 doi: 10.1007/s44197-024-00214-8

Brief Summary: This narrative review examined the potential role of telemedicine in improving care provision in low and middle income countries (LMICs), particularly for subspecialty pediatric care. There remain significant technological and regulatory obstacles, but the authors advocate for use of these innovations to promote equity and access to high quality pediatric care.

Delivering pediatric healthcare to rural communities can be challenging, particularly subspecialty care, and can create physical, psychological and financial burdens. New healthcare models using telemedicine may overcome barriers to access in remote and rural areas. Telemedicine has been used in developed countries for some time and the COVID pandemic made it more acceptable in LMICs, potentially having a higher impact in developing countries where resources are scarce, and cost of care is a major determinant of health. While telehealth runs concurrently to traditional healthcare models in high-income countries, it might be the only alternative in LMIC.

The authors note significant issues with implementation, including inadequate digital infrastructure. Low bandwidth telemedicine has been proven effective in overcoming poor network connectivity in Cambodia, Uzbekistan, and Kosovo, as shown in previous literature. With the high penetration of smart phones in low-income countries, focusing on phone-based interventions may decrease digital disparities. Phone-based applications can provide variable platforms for telemedicine including written consultations, audio or video consults.

Identifying providers with appropriate specialty training is also a challenge. There may be insufficient local specialists to remote care and international specialists may lack appropriate cultural understanding and awareness of the variability of locally available resources. Limited reimbursement for providers is also highly variable and many current services rely on volunteerism which may not be sustainable. However, telemedicine can also provide a tool for capacity building through shared decision-making and improving medical knowledge.

Despite many obstacles, the authors support the development of telemedicine to improve provision and decrease disparities in pediatric care and in LMICs.

14. The Year in Science and Medicine

Uğur Cem Yilmaz (*YES member*), Philipp Augsburger, Therina du Toit, Chrysanthi Kouri, Anne Smit, Isabel Sousa Barata, Ken K Ong, Christa E Flück

Introduction

This year's selection of articles for the chapter *"The Year in Science and Medicine"* highlights key advances in emerging and rapidly evolving fields, with a particular focus on artificial intelligence, long-read sequencing, metabolomics, steroidomics, and related interdisciplinary topics. The inclusion of selected high-impact studies reflects the growing influence of data-driven and systems-level approaches in biomedical research. Notably, the selection process was shaped organically through the collaborative efforts of the contributing authors, with each team member bringing forward compelling and timely publications. This serendipitous yet rigorous curation underscores the diversity and depth of innovation that characterized the scientific landscape over the past year.

Artificial Intelligence

14.1. A phenotype-based AI pipeline outperforms human experts in differentially diagnosing rare diseases using EHRs

Xiaohao Mao, Yu Huang, Ye Jin, Lun Wang, Xuanzhong Chen, Honghong Liu, Xinglin Yang, Haopeng Xu, Xiaodong Luan, Ying Xiao, Siqin Feng, Jiahao Zhu, Xuegong Zhang, Rui Jiang, Shuyang Zhang, Ting Chen

NPJ Digit Med. 2025;8(1):68.
doi: 10.1038/s41746-025-01452-1

Brief Summary: This study developed and evaluated PhenoBrain, an artificial intelligence (AI) pipeline for rare disease diagnosis using electronic health records (EHRs). It consists of two modules: 1) PBTagger, a deep learning-based Natural Language Processing (NLP) tool for extracting phenotypes from Chinese clinical texts, and 2) a differential diagnosis module using five novel machine learning models, including an Ensemble method. The system was tested on over 2,200 real and simulated cases from multiple international datasets and benchmarked against 50 physicians, ChatGPT, and GPT-4 in a controlled human-computer comparison.

This study addresses the global challenge of diagnosing rare diseases, which affect ~350 million people and are often misdiagnosed or diagnosed late. The authors introduce an AI system that automates phenotype extraction and disease ranking from EHRs. PhenoBrain outperformed 50 specialist physicians, ChatGPT, and GPT-4 in diagnostic accuracy across multiple datasets, achieving a top-3 recall of 0.61 and a top-10 recall of 0.81. When combined with human expertise, PhenoBrain further improved diagnostic performance, demonstrating its potential for integration into clinical workflows. It is also suggested to significantly reduce diagnostic delays and costs.

The study has several limitations, including the absence of multimodal data integration—such as genetic information, which is often essential for accurate rare disease diagnosis—and the current restriction to Chinese-language clinical texts. Furthermore, the diagnostic precision is constrained by incomplete or non-specific phenotype annotations available for many rare diseases.

Nevertheless, this study demonstrates that integrating AI predictions with physician expertise leads to superior diagnostic performance. Therefore, AI should be viewed not as a competitor, but as a collaborative partner in clinical decision-making.

14.2. Height estimation in children and adolescents using body composition big data: machine-learning and explainable artificial intelligence approach

Chun D, Chung T, Kang J, Ko T, Rhie YJ, Kim J
Digit Health. 2025;11:20552076251331879.
doi: 10.1177/20552076251331879

Brief Summary: This cross-sectional study provides a machine learning model using LightGBM and explainable AI techniques to estimate height in 54,374 children and adolescents aged 6–18 years based on body composition data from over 278,000 measurements. The model achieved high accuracy and identified soft lean mass (SLM), body fat mass percentage (BFMP), and skeletal muscle mass as key predictors. Explainable AI tools revealed interpretable relationships between body composition and height, offering insights into pediatric growth patterns.

This study underscores the clinical relevance of lean and fat mass in pediatric growth assessment, demonstrating their significant associations with height projections. While bone age-based height prediction remains the standard in routine clinical practice, this work introduces a novel approach by integrating multiple body composition variables for height estimation in children and adolescents.

However, the model's applicability is limited by the exclusion of other influential factors such as genetic background, lifestyle behaviors, socioeconomic status, and health conditions. To enhance generalizability and robustness, further studies are warranted to validate the model across diverse ethnic and socioeconomic populations and to incorporate longitudinal data.

Finally, comparative evaluations against existing growth prediction models will also be essential to establish its clinical utility.

14.3. Cost-effectiveness of AI for pediatric diabetic eye exams from a health system perspective

Ahmed M, Dai T, Channa R, Abramoff MD, Lehmann HP, Wolf RM
NPJ Digit Med. 2025;8(1):3.
doi.org/10.1038/s41746-024-01382-4

Brief Summary: In this modeling study the cost-effectiveness of implementing autonomous artificial intelligence (AI) for diabetic retinal disease (DRD) screening in pediatric patients was evaluated, comparing it to traditional eye care provider (ECP) exams from a U.S. health system perspective. The analysis shows that AI screening becomes cost-saving when a site screens at least 241 patients annually, with larger health systems benefiting more due to economies of scale. AI-based screening consistently results in more patients being screened and adhering to follow-up care, with improved cost-effectiveness as system size increases.

A recent review and meta-analysis evaluated the diagnostic performance of deep learning (DL) algorithms applied to optical coherence tomography (OCT) and retinal images for detecting DRD (1). Analyzing 47 studies, the authors found that DL models achieved high accuracy and sensitivity, with pooled odds ratios indicating significant improvements over traditional methods. The findings support DL's potential as a reliable, scalable tool for DRD screening to enhance early diagnosis and treatment, especially in resource-limited settings.

The study by Ahmed *et al*. demonstrates that AI screening can improve access, adherence, and equity in pediatric DRD care. Yet, the results are based on first-year implementation costs and may not reflect long-term savings. Also, some assumptions (e.g., patient behavior, cost estimates) may not generalize across all healthcare settings.

Thus, future studies should explore long-term cost-effectiveness, including downstream clinical outcomes. More granular analyses across diverse demographic, geographic, and insurance contexts are also needed. Additional research is required to assess AI effectiveness in routine care and in non-endocrine care settings.

Reference

1. Deep learning-based optical coherence tomography and retinal images for detection of diabetic retinopathy: a systematic and meta analysis. Bi Z, Li J, Liu Q, Fang Z. Front Endocrinol (Lausanne). 2025;16:1485311. DOI 10.3389/fendo.2025.1485311

14.4. Artificial intelligence is going to transform the field of endocrinology: an overview

Belkhouribchia J

Front Endocrinol (Lausanne). 2025;16:1513929.

doi: 10.3389/fendo.2025.1513929

Brief Summary: This opinion paper outlines how artificial intelligence (AI) is poised to revolutionize clinical endocrinology by enhancing risk assessment, diagnosis, personalized treatment, and remote patient monitoring. It provides an overview of the potential and future direction of AI in the domain of clinical endocrinology and diabetes.

The author presents a curated overview of recent studies showcasing the effectiveness of AI in various areas of endocrinology, including diabetes prediction, thyroid nodule assessment, metformin response optimization, and gestational diabetes management. While highlighting AI's transformative potential, the article also thoughtfully addresses the ethical, technical, and implementation challenges that must be overcome for successful clinical integration.

Emphasizing AI's role in advancing precision medicine and enhancing healthcare efficiency, the piece encourages clinicians to actively engage with emerging AI tools to improve patient outcomes and streamline care delivery.

Although the article is an opinion piece and does not offer a systematic review or original empirical data, its call to action for the endocrinology community to prepare for AI adoption is timely and well-founded.

Genomics – Long-Read Sequencing

14.5. Synchronized long-read genome, methylome, epigenome and transcriptome profiling resolve a Mendelian condition

Mitchell R. Vollger, Jonas Korlach, Kiara C. Eldred, Elliott Swanson, Jason G. Underwood, Stephanie C. Bohaczuk, et al

Nat Genet. 2025;57(2):469-79.

doi: 10.1038/s41588-024-02067-0

Brief Summary: This genetic case study used a synchronized long-read sequencing approach that simultaneously profiles the genome, CpG methylome, chromatin epigenome, and transcriptome from a single sample. It revealed the complex genetic disorder of a patient with an unsolved Mendelian condition. This method identified a balanced X;13 translocation that disrupted four genes (*NBEA*, *PDK3*, *MAB21L1*, and *RB1*), each through a distinct molecular mechanism. The integrated multi-omic strategy enabled the resolution of complex gene regulatory disruptions that would have been missed by conventional sequencing methods.

This study demonstrates the power of synchronized long-read multi-omic profiling to uncover the mechanistic basis of complex genetic disorders, especially those involving structural variants and non-coding regions. This approach is expected to empower clinicians and researchers with deeper insights into how various forms of genetic variation contribute to disease mechanisms, while also uncovering novel molecular targets for therapeutic intervention.

Further studies are needed to assess the generalizability of this approach across diverse genetic disorders and tissues. Furthermore, integration with clinical workflows and cost-effectiveness analyses is essential for broader adoption.

14.6. Integration of long-read sequencing, DNA methylation and gene expression reveals heterogeneity in Y chromosome segment lengths in phenotypic males with 46,XX testicular disorder/difference of sex development

Berglund A, Johannsen EB, Skakkebæk A, Chang S, Rohayem J, Laurentino S, Hørlyck A, Drue SO, Bak EN, Fedder J, Tüttelmann F, Gromoll J, Just J, Gravholt CH

Biol Sex Differ. 2024 Oct 8;15(1):77.

https://doi.org/10.1186/s13293-024-00654-8

Brief Summary: This integrative omics study investigated 11 individuals diagnosed with 46,XX testicular disorder/difference of sex development (DSD). By combining long-read sequencing, RNA-seq, and DNA methylation analyses, the authors identified four structural subtypes of Y chromosome translocations and demonstrated their association with distinct molecular and clinical phenotypes.

In rare sex development disorders such as 46,XX testicular DSD, structural genomic complexity often remains undetected by conventional diagnostic methods. The authors addressed this challenge using long-read sequencing technology, which enabled high-resolution mapping of Y chromosome breakpoints and subclassification into SRY-negative, short, medium, and long Yp arm subgroups.

The study identified variable deletions in the *PRKY, AMELY*, and *TBLY1* genes, and confirmed that most translocated PAR1 segments were of Y-chromosomal origin. Integration of epigenetic and transcriptomic data revealed that the length of the Y segment influenced not only Y-linked gene expression but also regulatory patterns on autosomal and X-linked genes. These molecular alterations were associated with clinical features such as short stature, reduced lean body mass, and small testicular volume.

These data strongly highlight the diagnostic and subclassification value of long-read sequencing in rare DSD cases. Although direct functional experiments (e.g., *in vitro* assays or protein-level studies) were not performed, the integration of genomic, transcriptomic, and epigenetic data revealed biologically meaningful patterns. This multi-omics approach sets a new standard for the molecular characterization of complex DSD phenotypes and facilitates more individualized clinical management.

14.7. Long-read sequencing solves complex structure of CYP21A2 in a large 21-hydroxylase deficiency cohort

Wang R, Luo X, Sun Y, Liang L, Mao A, Lu D, Zhang K, Yang Y, Sun Y, Sun M, Han L, Zhang H, Gu X, Qiu W, Yu Y
The Journal of Clinical Endocrinology & Metabolism, 110(2), 406–416. 2025.
doi.org/10.1210/clinem/dgae519

Brief Summary: This large original cohort study (n = 832) evaluated the diagnostic utility of long-read sequencing (LRS) in patients with 21-hydroxylase deficiency (21-OHD). LRS was applied to 152 cases where conventional methods had failed, successfully detecting complex *CYP21A2/TNXB* chimeric variants and clarifying ambiguous multi-copy genotypes.

The *CYP21A2 gene* lies within the highly homologous RCCX module and frequently undergoes recombination with its pseudogene *CYP21A1P*, making genetic diagnosis of 21-OHD particularly challenging. In this study, LRS not only identified all previously known chimeric subtypes but also uncovered six additional *CYP21A2* or *TNXB* chimeras missed by MLPA or Sanger sequencing. More than half of the 281 total chimeric alleles were detectable only by LRS, highlighting its unique diagnostic power. Thus, LRS emerges not merely as a complementary tool, but as an indispensable and potentially paradigm-shifting diagnostic technology.

The clinical relevance is also significant. *CAH-X (TNXA/TNXB* chimeras) was identified in 12.1% of patients, with biallelic carriers showing markedly more connective tissue features, such as joint hypermobility and skin hyperextensibility, compared to monoallelic carriers or CAH-X-negative individuals. This genotype-based stratification has direct implications for patient monitoring, genetic counseling, and multidisciplinary care planning.

Additionally, LRS enabled phasing of variants across duplicated *CYP21A2* alleles in eight patients, allowing accurate parental origin assignment. Its ability to simultaneously detect pathogenic variants in *CYP21A2* and in other key steroidogenesis genes (*CYP11B1, CYP17A1, HSD3B2, STAR*) supports its role as a comprehensive genotyping platform. Given its cost-effectiveness and added clinical value, the authors advocate LRS as a first-line diagnostic tool in CAH. Importantly, LRS also holds promise for other genetically complex adrenal disorders, such as P450 oxidoreductase deficiency and lipoid CAH, underscoring its expanding role in the molecular diagnosis of pediatric adrenal disorders. As long-read technologies become increasingly accessible, their routine integration into endocrine genetics workflows appears not only justified, but necessary.

14.8. Clinical evaluation of long-read sequencing-based episignature detection in developmental disorders

Mathilde Geysens, Benjamin Huremagic, Erika Souche, Jeroen Breckpot, Koenraad Devriendt, Hilde Peeters, Griet Van Buggenhout, Hilde Van Esch, Kris Van Den Bogaert, Joris Robert Vermeesch

Genome Med. 2025;17(1):1.
doi: 10.1186/s13073-024-01419-z

Brief Summary: These authors performed long-read whole genome sequencing (lrWGS; Oxford Nanopore technology) on 20 patients, representing 13 developmental disorders (DD) with known episignatures, and 40 controls to show proof-of-concept that lrWGS can simultaneously detect genomic variants (single nucleotide and structural variants) and disease-specific methylation signatures ("episignatures") in developmental disorders (DD).

Using lrWGS and hierarchical clustering, dimensionality reduction, and a custom support vector machine classifier, they correctly identified episignatures in 17 of 19 patients carrying (likely) pathogenic variants, with no false positives in the controls. The remaining two patients were classified as controls both by nanopore and microarray assays, demonstrating high concordance with standard methods. In addition, lrWGS successfully detected all underlying SNVs and structural variants and provided haplotype-aware analyses of X-chromosome inactivation and imprinting.

These findings show that lrWGS is an all-in-one diagnostic platform that is able to detect genetic variants, structural variants, and profile methylation; all in a single assay. As opposed to traditional diagnostics, which typically require multiple separate tests (e.g. exome sequencing, methylation assays and X-chromosome inactivation studies), lrWGS shows promise as a single comprehensive genetic assay that could streamline diagnostics, reduce costs and turnaround time, as well as patient burden. However, further development of long-read-specific episignature databases and classifiers is needed for broader clinical adoption.

14.9. Advancing long-read nanopore genome assembly and accurate variant calling for rare disease detection

Shloka Negi, Sarah L Stenton, Seth I Berger, Paolo Canigiula, Brandy McNulty, Ivo Violich, Joshua Gardner, Todd Hillaker, Sara M O'Rourke, Melanie C O'Leary, Elizabeth Carbonell, Christina Austin-Tse, Gabrielle Lemire, Jillian Serrano, Brian Mangilog, Grace VanNoy, Mikhail Kolmogorov, Eric Vilain, Anne O'Donnell-Luria, Emmanuèle Délot, Karen H Miga, Jean Monlong, Benedict Paten

Am J Hum Genet. 2025;112(2):428-49
doi: 10.1016/j.ajhg.2025.01.002

Brief Summary: This study evaluated the added diagnostic value of long-read sequencing (LRS) in a rare disease context using scalable Oxford Nanopore LRS. It generated high-quality sequences (with ~36× coverage and 32 kb read N50 per sample) of 98 individuals from 41 families. The custom "Napu" bioinformatics pipeline assembled complete genomes, phased variants, and assessed methylation, detecting ~280 genes and 5 known Mendelian disease-associated genes inaccessible to short-read sequencing (SRS). With LRS it also detected complex structural variants, tandem repeat expansions, and epigenetic alterations. Notably, 87% of protein-coding genes were fully phased, allowing confident interpretation of compound heterozygosity, de novo events, and mosaicism. The study achieved a molecular diagnosis in 11 probands with diverse genetic etiologies.

The study demonstrates that LRS can serve as a comprehensive, single-test alternative to traditional multi-step genetic diagnostics for rare disease diagnosis, showing its ability to detect a wide range of variant types, including those inaccessible to SRS, while also enabling phasing and methylation analysis in a single assay. Although some methylation outliers and structural variants could not be confidently linked to disease due to limited functional annotation.

The open-source Napu pipeline and cost-effective protocol pave the way for broader clinical adoption of LRS. But, LRS still has lower base-level accuracy than SRS, particularly for small indels in homopolymer regions, which may lead to missed or miscalled variants. Interpretation of LRS-exclusive variants is hindered by the lack

of long-read-specific population and clinical variant databases. Thus, larger, diverse population-scale LRS datasets are needed to improve variant interpretation and frequency estimation. Further development of somatic variant callers and tools for interpreting methylation and noncoding variation will enhance the diagnostic power of LRS in the future.

14.10. Toward clinical long-read genome sequencing for rare diseases

Eisfeldt J, Ek M, Nordenskjold M, Lindstrand A
Nat Genet. Jun;57(6):1334-1343 2025.
doi.org/10.1038/s41588-025-02160-y

Brief Summary: This "Perspective" outlines the roadmap for implementing long-read whole genome sequencing (LR-WGS) into clinical diagnostics for rare diseases. The authors highlight the advantages of long-read technologies in overcoming the limitations of short-read sequencing, particularly for detecting complex variants. The authors emphasize the value of generating haplotype-resolved genome assemblies and direct methylation profiling which are critical for the diagnosis of disorders caused by complex or non-coding variation. They also call for the development of standard protocols, quality metrics, and scalable analysis pipelines to enable the routine use of LR-WGS in healthcare settings at reasonable costs.

The paper underscores LR-WGS as a transformative technology that could unify genetic and epigenetic testing into a single, comprehensive diagnostic platform, potentially replacing multiple current methods. LR-WGS can detect previously inaccessible variant types (e.g., repeat expansions, balanced structural variants, methylation changes), thereby improving diagnostic yield for rare diseases. It enables more accurate variant interpretation through phasing and methylation profiling, especially in complex or mosaic cases. The authors suggest that national-scale implementation efforts could serve as models for global adoption.

Still, LR-WGS remains more expensive and labor-intensive than short-read sequencing, with lower throughput and greater computational demands. Its accuracy, particularly for detecting low-level mosaicism or somatic variants, still trails that of some short-read platforms. Moreover, bioinformatics tools and reference databases tailored to long-read data are still in early stages of development. Nevertheless, past advances in genetic technologies have shown that such challenges can be overcome.

14.11. Long-read next-generation sequencing for molecular diagnosis of pediatric endocrine disorders

Kuroki Y, Hattori A, Matsubara K, Fukami M
Annals of pediatric endocrinology & metabolism, 29(3), 156–160. 2024.
https://doi.org/10.6065/apem.2448028.014

Brief Summary: This mini-review outlines the application of long-read next-generation sequencing (long-read NGS) in the molecular diagnosis of pediatric endocrine disorders. It highlights various uses of platforms such as Oxford Nanopore Technologies and Pacific Biosciences—including detection of structural variants, repeat expansions, epigenetic changes, and haplotype phasing.

While short-read NGS and array-based CGH have revolutionized genetic diagnostics, they often miss complex structural variants, repeat expansions, and epigenetic abnormalities. Kuroki *et al.* demonstrate how long-read NGS helps overcome these limitations. Its extended read lengths enable detection of pathogenic variants that remain undetected by conventional methods. Examples include retrotransposon-related variants in *GNAS* and *NR5A1*, as well as chromothripsis-related rearrangements (e.g., massive genomic rearrangements caused by a single catastrophic event) seen in endocrine disorders.

A notable application is the *CYP21A2* region, associated with 21-hydroxylase deficiency, which is resistant to standard sequencing due to segmental duplications. Long-read NGS also facilitates methylation analysis without bisulfite treatment, useful for diagnosing imprinting disorders like Prader-Willi and Angelman

syndromes. Moreover, its haplotype phasing capacity allows for precise determination of compound heterozygosity and mosaic variant origin.

Several limitations persist, including higher base-calling error rates compared to short-read NGS, costs, technical complexity, and limited accessibility. However, recent advancements, such as adaptive sampling and rapid sequencing workflows, have significantly improved the accuracy, speed, and practicality of long-read NGS. As these innovations continue to evolve, long-read NGS is poised to become an indispensable diagnostic tool for rare or unexplained pediatric endocrine conditions and a cornerstone of future precision medicine.

Metabolomics, Steroidomics

14.12. Steroid hormone levels vary with sex, aging, lifestyle, and genetics

Deltourbe LG, Sugrue J, Maloney E, Dubois F, Jaquaniello A, Bergstedt J, Patin E, Quintana-Murci L, Ingersoll MA, Duffy D
Sci Adv. 2025 Mar 28;11(13):eadu6094.
doi: 10.1126/sciadv.adu6094

Brief Summary: In this human observational cohort study, involving 949 healthy adults, half male, half female, aged 20 to 69 years, the authors measured the levels of 17 steroid hormones by targeted mass spectrometry (MS), and investigated associations between steroid levels and biological sex, age, clinical and demographic data, genetics, and plasma proteomics. Furthermore, to identify associations between steroid hormone levels and health status, they assessed a subset (n = 415) of the original cohort 10 years after the initial study.

While confirming expected age- and sex-related hormone changes, such as the decline of estrogens in older women compared to younger individuals, the study also uncovered unexpected relationships. Oral hormonal contraception influenced circulating levels of multiple steroid hormones in women, while BMI and smoking were related to altered hormone levels in men only. Importantly, the finding that testosterone decline in men may be linked more to health status than to aging challenges prevailing assumptions about andropause.

The data highlight how socioeconomic and lifestyle factors, including housing, employment, and smoking habits, significantly correlate with hormone variations, underscoring the importance of considering these factors in medical research and treatment. The associations found between steroid hormones and genetic and plasma protein markers suggest new avenues for understanding hormone regulation.

Despite certain limitations, such as the genetic homogeneity of the cohort and measurement constraints, the study's findings are valuable for guiding future mechanistic studies. By revealing the complex interactions between hormones, sex, lifestyle, and health, this work has the potential to influence clinical management of hormone-related conditions and inform public health strategies. Overall, it lays a foundation for advancing research in endocrinology, metabolism, immunology, aging, and gender medicine contributing to a more holistic understanding of human health and how it might be shaped by environmental factors and gender behaviors.

14.13. Biological age prediction using a DNN model based on pathways of steroidogenesis

Wang Q, Wang Z, Mizuguchi K, Takao T
Sci Adv. 2025;11(11):eadt2624.
doi: 10.1126/sciadv.adt2624

Brief Summary: This study presents a novel deep neural network (DNN) model to predict biological age (BA) by integrating multi-omics data, with a focus on steroidogenesis pathway activity. The authors analysed 22 serum steroids from 148 healthy individuals aged 20 to 73 years, to develop and train the model. The DNN achieved accuracy for BA and identified cortisol as a key driver of aging and that smoking accelerates biological aging in males, highlighting the influence of lifestyle, sex/gender and stress-related hormones on aging.

This study introduces a biologically interpretable, pathway-based DNN model that advances the precision of biological age prediction by integrating steroid hormone metabolism, a critical but underutilized dimension in aging research. It shows that modeling steroidogenesis pathway activity can enhance biological age prediction, potentially providing a sensitive marker for early detection of physiological aging changes or monitoring interventions. By shifting the focus from passive chronological age to active biochemical processes, this study lays the groundwork for integrating functional endocrine biomarkers into the investigation of the multifaceted nature of aging and disease management.

On a larger picture, the suggested model provides a novel framework for personalized aging assessment using metabolomics. It demonstrates the utility of integrating biological pathways into machine learning models for improved interpretability and accuracy. It also offers potential for clinical applications in aging-related disease risk stratification and intervention monitoring.

The model relied on comprehensive serum steroid profiling, which may limit its applicability in settings with restricted biomarker availability. It did not account for circadian rhythms, dynamic physiological changes, or longitudinal fluctuations in serum steroid levels. Additionally, the study used a relatively small and demographically narrow sample and considered only limited lifestyle factors (e.g., smoking).

Further studies are needed to validate these findings, particularly in relation to environmental and behavioral influences as well as sex-specific differences.

14.14. Metabolomic fingerprints of clustered preterm and term neonates - a pilot study

Lorek M, Stradomska TJ, Siejka A, Fuchs J, Janus D, Gawlik-Starzyk A
Front Endocrinol (Lausanne). 2025;16:1569355.
doi: 10.3389/fendo.2025.1569355

Brief Summary: This prospective observational study on 50 preterm and full-term neonates utilized a steroid metabolomic signature approach, with metabolomic clustering revealing distinct adrenal steroid profiles associated with neonatal health outcomes, highlighting the complex interplay between steroidogenesis and clinical risks. K-means clustering was employed to distinguish three clusters among all neonates in the study, based on steroid profiling using gas chromatography-mass spectrometry of 24-hour urine collections. These three clusters differed in all adrenal steroid synthesis pathways, but not in prematurity, gestational age or birth weight.

The greatest variability among the clusters was related to DHEA and 17-hydroxyprogesterone metabolites. A decreased excretion for both C19 and C21 steroids was observed in Cluster 1, an increased excretion in Cluster 3, and moderately elevated excretion in Cluster 2. With regard to cortisol and cortisone derivatives, Cluster 2 exhibited high levels of excretion, while Cluster 3 demonstrated an intermediate level of excretion; however, Cluster 1 presented a significantly decreased result, with a statistical disparity when compared with Cluster 2. The study observed that neonates in Cluster 1 exhibited a marked reduction in steroids, indicating a profoundly diminished adrenal output. Collectively, these enzymatic patterns suggest a global suppression of neonatal steroidogenesis in Cluster 1, with emergency cesarean sections also significantly more frequent in Cluster 1 compared to Cluster 3. Ultimately, in Cluster 3, where steroidogenesis appears to be preserved, clinical outcomes were favorable.

These findings demonstrate the potential of metabolomic signatures to facilitate the stratification of neonates according to their adrenal steroid profiles, thus offering a promising avenue for the delivery of personalized neonatal care. The authors propose that individualized postnatal steroid replacement regimens could be optimized using each neonate's steroid metabolomic fingerprint, moving beyond uniform protocols based solely on gestational age. By leveraging AI-driven analytics, clinicians could more accurately identify, classify, and predict high-risk neonatal phenotypes, thus enhancing diagnostic precision and ultimately improving patient outcomes.

14.15. Neonatal reference intervals for serum steroid hormone concentrations measured by LC-MS/MS

Anouk Olthof, Jolanda C Naafs, Nitash Zwaveling-Soonawala, Charlotte A Heinen, Sabine E Hannema, Jacquelien J Hillebrand, Anita Boelen, Paul AS, van Trotsenburg, Annemieke C Heijboer
Clin Chem Lab Med. 2025;63(4):805-11.
doi: 10.1515/cclm-2024-0393

Brief Summary: In this study, serum steroids of healthy term neonates were measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS) at two timepoints (130 samples at day 3–8 (T1) and 126 samples at day 13–15 (T2)) to establish reference intervals (RIs) for serum cortisol, cortisone, corticosterone, 11-deoxycortisol, 21-deoxycortisol, 11-deoxycorticosterone, testosterone, androstenedione, and 17-hydroxyprogesterone. These RIs are intended to improve the diagnostic accuracy of conditions like congenital adrenal hyperplasia (CAH) and differences of sex development (DSD) in neonates.

Age- and sex-specific neonatal RIs for steroid hormones are essential for accurate interpretation of diagnostic results during the neonatal period. Although chromatographic-mass-spectrometric methods are considered the gold standard for measuring steroid hormones, RIs for these hormones in serum have been lacking so far for neonates, particularly during the first two weeks of life, when abnormal screening results require reliable laboratory diagnostics. Establishing these RIs is crucial to support the transition from immunoassay-based to LC-MS/MS-based diagnostics, which offer superior specificity and accuracy.

The study was 'only' able to establish RIs for 9 serum steroids as for some hormones (e.g., 21-deoxycortisol, 11-deoxycorticosterone) concentrations were below the lower limit of quantification (LLOQ).

Further studies are needed to establish RIs in preterm and low-birth-weight neonates. Expansion to include additional steroid hormones could improve diagnostic coverage for rarer endocrine disorders. In addition, longitudinal data beyond the first two weeks of life would help understand hormone dynamics during early infancy and provide RIs for controlling treatment success in infants with disorders of steroid biosynthesis.

14.16. Impaired 11β-hydroxysteroid dehydrogenase type 2 activity in kidney disease disrupts 11-oxygenated androgen biosynthesis

Maria Tomkins, Tara McDonnell, Leanne Cussen, Michael S Sagmeister, Imken Oestlund, Fozia Shaheen, Lorraine Harper, Rowan S Hardy, Angela E Taylor, Lorna C Gilligan, Wiebke Arlt, Marie McIlroy, Declan de Freitas, Peter Conlon, Colm Magee, Mark Denton, Conall O'Seaghdha, Jacky L Snoep, Karl-Heinz Storbeck, Mark Sherlock, Michael W O'Reilly
The Journal of Clinical Endocrinology & Metabolism. 110, 1701–1715 (2025)
doi: 10.1210/clinem/dgae714

Brief Summary: This study demonstrates that chronic kidney disease (CKD) impairs the activity of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2), which is essential for the biosynthesis of active 11-oxygenated androgens. Using a combination of clinical data (e.g. cross-sectional, observational study of serum and urinary steroid profiles of 85 patients and 46 healthy controls), enzyme kinetics, and computational modeling, the authors show that reduced HSD11B2 activity in CKD leads to decreased conversion of 11β-hydroxyandrostenedione (11OHA4) to its active metabolites, including 11-ketotestosterone (11KT).

This is the first *in vivo* study to confirm the critical role of renal HSD11B2 in the biosynthesis of 11-oxygenated androgens, a class of potent androgens increasingly recognized for their role in health and disease. Estimated HSD11B2 expression was positively correlated with estimated glomerular filtration rate and could be clustered based on the disease stage. In addition, the relative contribution of 11OHA4 to the total circulating 11-oxygenated androgen pool increased with progression of CKD disease stage, indicating a build-up of precursor due to impaired HSD11B2 activity. These findings confirm that the kidney is a major site of HSD11B2 expression and activity. The decrease in circulating 11-oxygenated androgens might play a role in the progression of CKD and should be investigated in the future. The computational model developed could be used to monitor disease progression or predict endocrine outcomes in CKD.

In a broader context, the study establishes a novel link between kidney function and peripheral androgen metabolism. It suggests that 11-oxygenated androgen deficiency may contribute to CKD-associated conditions such as anemia, sarcopenia, and frailty.

Study limitations include a) age and sex differences between CKD and control groups, b) urinary steroid measurements may be less reliable in advanced CKD due to altered renal excretion, c) cross-sectional study design limits causal inference regarding androgen deficiency and clinical outcomes.

Other Topics

14.17. Androgens modulate the immune profile in a mouse model of polycystic ovary syndrome

Sara Torstensson, Angelo Ascani, Sanjiv Risal, Haojiang Lu, Allan Zhao, Alexander Espinosa, Eva Lindgren, Maria H Johansson, Gustaw Eriksson, Maya Barakat, Mikael CI Karlsson, Camilla Svensson, Anna Benrick, Elisabet Stener-Victorin
Advanced Science. 11, 2401772 (2024).
doi: 10.1002/advs.202401772

Brief Summary: In a PCOS-like mouse model, this study uses a combination of flow cytometry, ELISA, and metabolic phenotyping to show the effect of hyperandrogenism on immune cell populations in a tissue-specific manner. Androgen exposure caused a decrease of eosinophils in the uterus and visceral adipose tissue as well as a higher frequency of natural killer cells and elevated levels of IFN-γ and TNF-α in the uterus. Using an androgen receptor antagonist, these results were mitigated, leading to the conclusion that these effects were dependent on androgen receptor activation.

Despite the PCOS-like mice having an altered immune profile in visceral adipose tissue, as well as a higher body weight, their fat mass was unaltered compared to control mice. Moreover, androgen-exposed mice were insulin-resistant, mimicking a common PCOS-like trait.

These findings show that hyperandrogenism directly influences immune cell composition in reproductive and metabolic tissues leading to impaired tissue function. Moreover, the immunological disturbances discovered in androgen-exposed mice provide insight into how PCOS and low-grade inflammation are associated with each other. The study highlights the importance of considering immune dysregulation in PCOS pathophysiology and suggests that targeting androgen receptor signaling could be a therapeutic target to mitigate both reproductive and metabolic complications in PCOS patients.

Limitations: The study is based on a mouse model; thus human validation is needed. The exact mechanisms by which AR signaling indirectly affects non-AR-expressing immune cells remain unclear and the functional consequences of immune alterations on fertility and metabolism were not directly tested.

14.18. An expanded metabolic pathway for androgen production by commensal bacteria

Taojun Wang, Saeed Ahmad, Angélica Cruz-Lebrón, Sarah E Ernst, Kelly Yovani Olivos Caicedo, Yoon Jeong, et al
Nat Microbiol. 2025;10(5):1084-98.
doi: 10.1038/s41564-025-01979-9

Brief Summary: This *in vitro* and *ex vivo* study combined microbial genetics, *in vitro* cancer cell assays, and an observational cohort study of 69 patients with hormone-sensitive prostate cancer (HSPC). It elucidated a novel bacterial pathway for androgen biosynthesis from host-derived glucocorticoids, identifying microbial 17α and 17β-hydroxysteroid dehydrogenases (DesF and DesG) that produce active androgens, including

epitestosterone (epiT) and testosterone (T). The authors demonstrate that these microbial metabolites can activate androgen receptor (AR) signaling and promote prostate cancer cell proliferation, even in the presence of androgen deprivation therapy (ADT) and abiraterone. They also show that these genes are enriched in the gut and urinary microbiota of patients with advanced prostate cancer, suggesting a potential microbial contribution to disease progression and therapy resistance.

The conversion of glucocorticoid derivatives to androgens by microbial strains was confirmed using liquid chromatography-mass spectrometry and nuclear magnetic resonance. Comparative genomics and RNA-seq analysis identified the bacterial genes *desF* and *desG* as encoding enzymes responsible for the synthesis of epiT and 11β-hydroxy-testosterone, respectively. Challenging the long-held standing dogma that epiT is an inactive androgen, epiT is shown here to be produced by gut bacteria from commonly used glucocorticoids and to promote proliferation of androgen-sensitive prostate cancer cells while sustaining AR target gene expression. Elevated *desF* levels associated with HSPC progression suggest that gut microbiota-mediated androgen synthesis may undermine the efficacy of ADT therapy. Notably, the alternative bacterial androgen biosynthesis pathway seems to be not inhibited by abiraterone, a drug that blocks human androgen production, highlighting a potentially targetable mechanism for overcoming abiraterone resistance.

Overall, this study underscores the growing importance of the microbiome in cancer therapy. The findings warrant further investigation into whether long-term colonization of the urinary tract or gut by androgen-producing bacteria may be associated with cancer risk, disease progression in certain individuals, or contribute to other endocrine-related conditions. If confirmed, these insights could open new avenues for microbiome-targeted therapies in hormone-driven cancers.

14.19. A comprehensive spatio-cellular map of the human hypothalamus

Tadross JA, Steuernagel L, Dowsett GKC, Kentistou KA, Lundh S, Porniece M, Klemm P, Rainbow K, Hvid H, Kania K, Polex-Wolf J, Knudsen LB, Pyke C, Perry JRB, Lam BYH, Brüning JC, Yeo GSH
Nature. 2025 Mar;639(8055):708-716.
doi: 10.1038/s41586-024-08504-8

Brief Summary: This human cell and molecular atlas study used data from post-mortem tissue from 8 brain donors of normal body mass index (BMI). It combined single-nucleus RNA sequencing (snRNA-seq) and spatial transcriptomics on 433,369 human hypothalamic cells to create a comprehensive transcriptional map of the hypothalamus ("HYPOMAP"). The study is comparative (human vs. mouse), cross-sectional, and includes genomic association analysis with BMI.

While most prior knowledge in hypothalamic research stems from mouse models, HYPOMAP bridges this gap by offering detailed molecular and spatial characterization of human hypothalamic cell types, including previously overlooked non-neuronal populations such as astrocytes, oligodendrocytes, and ependymal cells. By precisely localizing key hypothalamic neurons and non-neuronal cell types involved in appetite regulation and metabolic control, this work bridges molecular endocrinology and neuroanatomy. Notably, the identification of distinct incretin receptor-expressing neuronal populations and the refined mapping of leptin–melanocortin circuits illuminate potential pathways through which steroid hormones might influence energy homeostasis and body weight regulation. This integration of cellular resolution data with systemic hormone profiles promises to enhance understanding of the hypothalamic role for sex- and age-related differences in metabolism and offers a robust platform for developing targeted interventions in metabolic disorders.

While the study is limited by a modest number of donors and an underrepresentation of sex, younger ages and disease diversity, the presented dataset provides a robust baseline for future research into hypothalamic dysfunction in obesity, metabolic disorders and beyond. To encourage further studies, the dataset is openly available.

14.20. Causal machine learning for single-cell genomics

Tejada-Lapuerta A, Bertin P, Bauer S, Aliee H, Bengio Y, Theis FJ
Nat Genet. 2025;57(4):797-808.
doi.org/10.1038/s41588-025-02124-2

Brief Summary: This 'Perspective' article outlines how causal machine learning (CML) can be applied to single-cell genomics to uncover mechanistic insights into cellular processes. The authors discuss the limitations of current statistical learning approaches and propose causal models that can generalize across experimental conditions, interpret biological mechanisms, and capture temporal dynamics. They highlight three major challenges: 1) generalization to novel perturbations, 2) interpretability of learned models, and 3) modeling of dynamic cellular processes.

Integrating causal inference into single-cell biology offers the opportunity to develop models of gene regulation and cellular behavior, supporting drug discovery and experimental design. It encourages the use of interpretable models that align with known biological pathways, regulatory mechanisms, and disease processes.

Limitations: Current causal models often rely on assumptions, such as perfect interventions, that may not hold in real biological systems, which are typically more complex, involving multimodal and spatiotemporal dynamics. Additionally, there is a lack of large, standardized, and high-quality interventional datasets needed to effectively train and validate these models.

15. Editors' Choice

Ken K. Ong, Christa E. Flück

Preface

I (KKO) began contributing to the *Yearbook of Paediatric Endocrinology* in 2004 as editor of the former chapter on "*Population Genetics*". A measure of success of that chapter, like the one on "*Evidence-based Medicine*", was that these topics became ingrained in the contents of all other chapters, and a stand-alone chapter on genetics was no longer included since 2012. However, there has been such rapid recent progress in genetics research tools, analytical approaches, mechanistic understanding and clinical insights that I make no apology in assigning a large proportion of this current chapter to genetics. Not only researchers but also clinicians need to keep informed of the rapidly expanding use of genetics in both research and clinical care.

Of the other papers, I urge you to note the papers on screening for food insecurity (15.14) and on the impact of retracted publications on systematic review evidence and clinical guidelines (15.15).

Genetics

15.1. Lifesaving diagnosis through prenatal genomic sequencing

Fennell AP, Roscioli T, Buckley M, Horton AE, Long S, Pharande P, Clucas LM
N Engl J Med 2025;393:93-95.
PMID: 40601945 doi: 10.1056/NEJMc2506080

In Brief: This case report describes the management of a male infant born after prenatal genetic diagnosis of congenital thrombotic thrombocytopenic purpura (TTP) resulting in marked thrombocytopenia (platelet count, 8×10^9/L) and severe hyperbilirubinemia. Antenatal diagnosis allowed urgent lifesaving interventions to be started within the first hour after birth. On follow-up at age 17 months, growth, development, and cardiac, renal, and hepatic function were normal.

Comment: This remarkable case report describes the power of anticipatory genetic testing to allow the timely implementation of essential, lifesaving healthcare. Prenatal trio exome sequencing had been undertaken at 31 weeks gestation to investigate left ventricular dilatation on antenatal ultrasound scan. This revealed the diagnosis of filamin C (FLNC)-related cardiomyopathy. A second, incidental genetic diagnosis of congenital TTP was made, due to compound heterozygous missense variants in *ADAMTS13* (his ADAMTS13 activity measured at birth was $<1\%$).

Congenital TTP is a severe, early-onset but treatable condition, and this newborn showed early radiographic evidence of microangiopathy, indicatingperipartum or prenatal sequelae of the disease. Early imaging showed a chronic internal jugular veinthrombosis, cerebral punctate haemorrhagic venous infarcts, small subdural haemorrhages, and appearance consistent with thrombosed small veins. He was given fresh frozen plasma (FFP) and intensive phototherapy within the first hour after birth. FFP was continued every 4-6 hours until Day 12 of life. He also had a platelet transfusion on Day 2 of life due to gastrointestinal bleeding. Coincidentally, recombinant ADAMTS13 therapy was approved by the US Food and Drug Administration only days before his delivery, but was available (on compassionate grounds) only from Day 15 onwards. This was continued weekly and the child has since been free of further TTP exacerbations.

15.2. Phase 1 trials of PNPLA3 siRNA in I148M homozygous patients with MAFLD

Fabbrini E, Rady B, Koshkina A, Jeon JY, Ayyar VS, Gargano C, DiProspero N, Wendel S, Hegge J, Hamilton H, Ding ZM, Afrazi M, Nicholas A, Pei T, Nakano M, Ouchi S, Saito Y, Yamashita A, Tamamura R, Salazar H, Shapiro C, Yoshihara T, Yonemura T, Inoue S, Matsuoka O, Erion M, Pocai A, Makimura H

N Engl J Med 2024; 391:475-476.
PMID: 39083780 doi: 10.1056/NEJMc2402341

In Brief: This Phase 1 randomised controlled trial tested a single subcutaneous injection of JNJ-75220795, a siRNA (molecular inhibitor) against *PNPLA3*, in participants who were homozygous ($n=40$) or heterozygous ($n=24$) for the I148M genetic variant in *PNPLA3*. Dose-dependent reductions in liver fat content were seen in homozygous but not heterozygous participants, apparent at 6 weeks, peaked at 12 weeks (46% reduction) and sustained for at least 24 weeks. No safety issues were identified.

Comment: This successful new intervention targeting the gene, *PNPLA3* (patatin-like phospholipase domain-containing 3), builds on work that originally identified *PNPLA3* through a genome-wide association study (GWAS) for metabolic dysfunction-associated fatty liver disease (MASLD) (1). The *PNPLA3* risk allele, I148M, disrupts enzymatic lipolysis activity on lipid droplets in hepatocytes, and thereby confers MASLD. Homozygotes for *PNPLA3* I148M are more severely affected and have increased susceptibility to liver fibrosis, cirrhosis, and hepatocellular carcinoma. In previous studies, JNJ-75220795, a siRNA against *PNPLA3*, resulted in sustained silencing of *PNPLA3* mRNA. Future studies are needed to characterise the duration of effect and optimal dosing and frequency of JNJ-75220795.

Despite well-recognised limitations of GWAS findings to pinpoint causative genes and mechanisms of disease, its use and wealth of findings continue to grow and there are increasing examples of mechanistic and treatment insights.

Reference

1. Romeo S *et al.* Genetic variation in *PNPLA3* confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008; 40(12):1461-5. doi: 10.1038/ng.257.

15.3. The genetic basis of human height

Louise S. Bicknell, Joel N. Hirschhorn, Ravi Savarirayan

Nature Reviews Genetics 2025 Apr 7. Online ahead of print. PubMed: 40189669
https://doi.org/10.1038/s41576-025-00834-1

In Brief: This review article summarises and beautifully illustrates recent progress in the common and rare genetic determinants of human height, and the resulting mechanistic insights. It shows how findings from different study designs (rare monogenic cases through to large population-based studies) converge on the same genes and pathways, and how these inform new treatment targets for rare skeletal disorders.

Comment: Human height (in particular adult height) has long been considered the exemplar phenotype for genetics studies due to its very high heritability: estimated $>80\%$ with only $<20\%$ due to environment. Therefore, while this topic is of particular relevance to Paediatric Endocrinologists, height is also a useful trait to illustrate the value of recent advances in the studies of both common and rare genetic variants.

There are now a remarkable 12,111 independent common genetic 'signals' identified through genome-wide association studies (GWAS) that have pooled data on millions of participants. Indeed, these studies have now reached 'saturation', at least in European ancestry populations. But this explains only ~50% of heritability. The remaining heritability is likely due to 'low frequency' variants that are being increasingly revealed by genome sequence data in large population studies and these findings will shed light on yet unidentified 'very rare' monogenic disorders.

While studies of syndromic short stature have identified mutations in several components of the growth hormone-IGF-1 pathway (*GH1, IGF1, IGF2, IGF1R, GHR, STAT3, STAT5, IGFALS*), most of the mechanisms targeted by genetic findings are skeletal. The authors highlight various core cellular processes that regulate

bone plate function, including: DNA Replication Cell cycle progression, DNA damage response & DNA repair, and several epigenetic regulators. Finally, they describe how genetic evidence for *CNP* and *NPR2* affecting the regulation of *FGFR3* support new and emerging treatments for achondroplasia.

15.4. Yield of genetic association signals from genomes, exomes and imputation in the UK Biobank

Gaynor SM, Joseph T, Bai X, Zou Y, Boutkov B, Maxwell EK, Delaneau O, Hofmeister RJ, Krasheninina O, Balasubramanian S, Marcketta A, Backman J, Regeneron Genetics C, Reid JG, Overton JD, Lotta LA, Marchini J, Salerno WJ, Baras A, Abecasis GR, Thornton TA

Nat Genet 2024; 56:2345-2351.
PMID: 39322778 doi: 10.1038/s41588-024-01930-4

In Brief: This population-based study in up to 468,169 UK Biobank participants compared the genetic contributions to 100 complex traits arising from different types of data: whole-genome sequencing (WGS), whole-exome sequencing (WES) and array genotyping with imputation (IMP). Compared to WES + IMP, WGS generated data on ~5-times more genetic variants but resulted in a very modest increase in the number of robust genetic associations (only 1% more).

Comment: Substantial public, charitable and commercial funding continues to sustain a remarkable pace of growth in genetic research data, with much of it being available in the public domain. WGS is by definition the most complete source of germline genetic information. WES (which sequences only protein coding domains) and IMP (genotyping of a subset of tagging variants then statistical estimation of the others) were designed as affordable alternatives while the cost of WGS was prohibitive.

In an era when all 3 sources are now available (WGS, WES and IMP), it may seem surprising then that WES + IMP are the preferred options to WGS. There are several reasons for this. The authors focussed on complex traits, which are likely to be polygenic in origin. By contrast, WGS is likely most informative for studies of rare monogenic disorders. Second, current affordable WGS uses short-read sequencing and has lower coverage than clinical sequencing. This reduces its accuracy and it does not detect large structural variations. Third, WGS provides the most complete 'search space' (compared to WES and IMP) but in doing so it requires the most stringent statistical thresholds to control against multiple testing and false positive findings. WGS will (by definition) provide the most complete genetic picture but (at least for complex traits) will require far larger samples sizes than we have now.

15.5. Dissecting the reduced penetrance of putative loss-of-function variants in population-scale biobanks

David R. Blair, Neil Risch

medRxiv preprint, September 24, 2024.
https://doi.org/10.1101/2024.09.23.24314008

In Brief: The authors analysed genetic data from 2 population-scale studies, the UK Biobank and All of Us (USA), to identify reasons for the low penetrance of loss-of-function variants (LoF) on disease risks. While study biases are part of the answer, improved prediction of LoF variant pathogenicity also increases the observed impacts on disease risks.

Comment: There is a major discrepancy between the genetic findings from rare disorders and their families vs those of the same variants in large population-based studies. In the former, these variants invariably have 'complete penetrance' (all carriers exhibit evidence of the relevant disease). But in the latter, levels of penetrance are very often lower than 50%. This discrepancy is important with increasing use of genetic screening in (yet) unaffected individuals, as well as the interpretation of incidental findings on genetic testing of patients.

Some of this is due to the quality of data collected by huge research 'biobanks', for example which may not include relevant phenotypes or rely on routine clinical data and self-reports. However, another reason identified

here is we may be too lenient about which LoF variants are classified as pathogenic and therefore reported in clinical test results. Stop-gain, frameshift and splice change variants are all grouped as LoF; we should recognise that the former group have more consistent and larger disruptions on gene function. Even among stop-gain variants, those that result in larger numbers of amino acids lost will have larger impacts on disease risk.

The next time you get a clinical test report of a pathogenic variant, think to ask how pathogenic it is.

15.6. Combining evidence from human genetic and functional screens to identify pathways altering obesity and fat distribution

Baya NA, Erdem IS, Venkatesh SS, Reibe S, Charles PD, Navarro-Guerrero E, Hill B, Lassen FH, Claussnitzer M, Palmer DS, Lindgren CM

medRxiv March2025. [Preprint].

PMID: 39371160 www.medrxiv.org/content/10.1101/2024.09.19.24313913v2

In Brief: The authors analysed whole exome-sequencing data from 402,375 UK Biobank participants to identify 19 genes in which rare, predicted loss-of-function damaging variants are associated with overall body fat or region-specific fat distribution (BMI, body fat percentage and waist-hip ratio, WHR). They performed experimental CRISPR knockdown of 14 genes in human white adipose tissue cell lines to confirm their cellular impacts on lipid accumulation.

Comment: Even with significant advances in statistical genetics and bioinformatics predictions of gene and variant function (see comment in this chapter on *Blair & Risch, medRxiv 2024*), experimental confirmation of the predicted functional impacts remains mandatory. The authors apply state of art cellular knock down and phenotyping to validate the findings of population-based genetics studies. The authors used the high throughput Opera Phenixcell phenotyping system to detect BODIPY staining, a marker of both lipid accumulation and adipogenesis more generally, as well as RNA sequencing to detect the impacts on expression of individual genes and gene pathways. There was statistically highly significant ($P = 4 \times 10^{-6}$), but numerically only moderate overlap (3 genes: *PPARG*, *PLIN1*, and *MC4R*) with the 31 genes known to cause severe monogenic obesity or lipodystrophy.

Another strength of the study was the assessment of the identified variants on detailed parameters of body fat distribution, measured by both DEXA and whole body MRI, although unfortunately these traits were measured in $< 10\%$ of the full study sample. Interestingly, in sex-specific analyses, rare variants in *INSR* decreased WHRadjBMI in females but increased WHRadjBMI in males. Unfortunately, experimental *INSR* knockdown was incomplete (*INSR* remained partially expressed) and no impact on lipid accumulation was detected in this model.

15.7. Multivariate genomic analysis of 5 million people elucidates the genetic architecture of shared components of the metabolic syndrome

Park S, Kim S, Kim B, Kim DS, Kim J, Ahn Y, Kim H, Song M, Shim I, Jung SH, Cho C, Lim S, Hong S, Jo H, Fahed AC, Natarajan P, Ellinor PT, Torkamani A, Park WY, Yu TY, Myung W, Won HH

Nat Genet 2024; 56:2380-2391.

PMID: 39349817 doi: 10.1038/s41588-024-01933-1

In Brief: The authors perform a large multivariate genome-wide association analysis (GWAS) of components of the metabolic syndrome (MetS) in nearly 5 million individuals. They identify 1,307 independent genetic signals, which are primarily expressed in brain tissues. They analyse transcriptomic data, perform phenome-wide association and Mendelian randomization analyses to highlight associations of MetS with diverse non-cardiometabolic diseases.

Comment: Multivariate (GWAS) is a powerful statistical approach, which leverages information from multiple related traits. It is a particularly relevant approach to study conditions such as Mets, where the definition relies on contributions from different but related traits (i.e. measures of central obesity, dyslipidemia, hypertension and

impaired glucose tolerance). By doing this, the authors report by far the largest GWAS for MetS to date. As well as the expected genetic relevance of MetS to obesity, diabetes and cardiovascular disease, unexpected links were identified with renal (e.g. renal failure and urinary tract infection), respiratory (e.g. pneumonia) and mental disorders (e.g. tobacco use and anxiety disorders).

The study provides a rich 'treasure trove' of statistical genetics results, which will hopefully inform future experimental work to understand the mechanisms that lead to MetS, particular those underlying their (surprising) enrichment for gene expression in the brain.

15.8. Genetic architecture of oral glucose-stimulated insulin release provides biological insights into type 2 diabetes aetiology

Madsen AL, Bonas-Guarch S, Gheibi S, Prasad R, Vangipurapu J, Ahuja V, Cataldo LR, Dwivedi O, Hatem G, Atla G, Guindo-Martinez M, Jorgensen AM, Jonsson AE, Miguel-Escalada I, Hassan S, Linneberg A, Ahluwalia TS, Drivsholm T, Pedersen O, Sorensen TIA, Astrup A, Witte D, Damm P, Clausen TD, Mathiesen E, Pers TH, Loos RJF, Hakaste L, Fex M, Grarup N, Tuomi T, Laakso M, Mulder H, Ferrer J, Hansen T
Nat Metab 2024; 6:1897-1912.
PMID: 39420167 doi: 10.1038/s42255-024-01140-6

In Brief: The authors performed genome-wide association study (GWAS) analyses for 8 OGTT-based measures of β-cell function in ~26,000 individuals of European descent. They integrated the 55 independent genetic signals with pancreatic islet transcriptomic and epigenomic datasets to prioritise 92 candidate genes. Gene silencing in β-cell models highlighted *ACSL1* and *FAM46C* as novel regulators of insulin secretion.

Comment: This paper is an excellent example of integrating expertise in insulin secretion physiology, statistical genetics, bioinformatics informed by molecular data from the exact tissue of interest, together with experimental gene knock-down in cell lines and data from gene knock-out mice. It identifies and characterises many known or expected genes (e.g.*GIPR*, *IGF2BP2*, *TCF7L2*) and also many previously unknown loci, which may represent future drug targets.

In particular, their findings highlight *ACSL1*, which encodes the long-chain fatty acyl-CoA synthetase 1 and which may impact insulin release by altering the fatty acid composition of insulin granules and mitochondrial function. Also, *FAM46C* (family with sequence similarity 46, member C), whose expression levels were correlated with glucagon and islet amyloid polypeptide (IAPP, or 'amylin'), as well as with expression levels of genes involved in insulin exocytosis (*SYT13*, *SYT16*, *STXBP4*), proinsulin processing (*PCSK1*, *CPE*) and β-cell differentiation (*NEUROD1*).

15.9. Whole-genome sequencing analysis identifies rare, large-effect noncoding variants and regulatory regions associated with circulating protein levels

Hawkes G, Chundru K, Jackson L, Patel KA, Murray A, Wood AR, Wright CF, Weedon MN, Frayling TM, Beaumont RN
Nat Genet 2025; 57:626-634.
PMID: 39994471 doi: 10.1038/s41588-025-02095-4

In Brief: To examine the contribution of rare noncoding genetic variants to biology and disease risks, the authors analysed whole-genome sequencing (WGS) data consisting of 1.1 billion variants to identify associations with circulating levels of 2,907 proteins in ~50,000 UK Biobank participants. They identify 604 rare noncoding single-variants associated with circulating protein levels.

Comment: To date, the large majority of disease-altering mutations are in gene-coding sequences, which may disrupt the production, stability or function of that gene. Such mutations are detectable on gene-centric assays, including whole exome sequencing (WES). By contrast, WGS generates far greater datasets; 98-99% of the genome is noncoding. A major challenge is to determine which of those noncoding genetic variants might have functional consequences.

The authors undertake a clever approach to address this question, hypothesising that functionally relevant noncoding variants may alter circulating protein levels. This approach takes advantage of widely-available data from the UK Biobank on WGS and also 'proteomics' generated by Olink technology. Noncoding variants associated with protein levels were more likely to occur in regions near to genes, in 5′-UTR and predicted intronic splice acceptor or donor sites, which are not captured by WES. Observed effect sizes were as large as those seen for rare coding variants.

A crucial warning for those using UK Biobank WGS data is that only one-third of measured proteins had what the authors considered 'high-quality WGS data' across the relevant gene's locus, indicating limited quality of the efficiently produced 'low coverage' WGS. Further resources are needed to generate 'high coverage' WGS data at large scale, as well as more comprehensive proteomic measurements.

Obesity

15.10. Tirzepatide as compared with semaglutide for the treatment of obesity

Aronne LJ, Horn DB, le Roux CW, Ho W, Falcon BL, Gomez Valderas E, Das S, Lee CJ, Glass LC, Senyucel C, Dunn JP, Investigators ST

N Engl J Med 2025; 393:26-36.
PMID: 40353578 doi: 10.1056/NEJMoa2416394

In Brief: This open-label, trial randomised 751 adults with obesity and without type 2 diabetes to receive tirzepatide (10 mg or 15 mg) or the maximum tolerated dose of semaglutide (1.7 mg or 2.4 mg) subcutaneously once weekly for 72 weeks. Percent weight loss was greater on tirzepatide (−20.2%; 95% confidence interval −21.4 to −19.1) than on semaglutide(−13.7%; −14.9 to −12.6). Nausea was the most common side-effect, in 44% of participants in both treatment arms, and led to treatment discontinuation in 2.7% on tirzepatide and 5.6% on semaglutide. The trial was funded by Eli Lilly, the manufacturer of tirzepatide.

Comment: Drugs that target incretin receptors have emerged as transformative treatments for obesity. The main targets are glucagon-like peptide-1 (GLP-1) receptors and glucose dependent insulinotropic polypeptide (GIP) receptors. Semaglutide is a long-acting GLP-1 receptor agonist. This trial substantiates the premise to develop tirzepatide, that dual agonism of both the GIP and GLP-1 receptors, which have both overlapping and nonoverlapping expression and function, is more effective than agonism of each receptor alone.

This 'head-to-head' trial of 2 highly successful drugs has been eagerly awaited. In 2024, semaglutide-based products (Wegovy, Ozempic, Rybelsus) generated approximately US $28.4 billion worldwide, compared to $16.5 billion for tirzepatide. Tirzepatide ('Mounjaro') has been dubbed the '*King Kong*' of weight loss drugs. However, (like in the movie) tirzepatide faces stiff and increasing competition by new and emerging treatments. Retatrutide is a triple agonist, adding targeting of glucagon receptors to GIP and GLP-1, and has been dubbed the '*Godzilla'* of weight-loss injections! As well as effectiveness, other new agents may bring fewer side-effects or easier oral route of administration. The prospect of such future developments is promising for our patients.

15.11. NK2R control of energy expenditure and feeding to treat metabolic diseases

Sass F, Ma T, Ekberg JH, Kirigiti M, Urena MG, Dollet L, Brown JM, Basse AL, Yacawych WT, Burm HB, Andersen MK, Nielsen TS, Tomlinson AJ, Dmytiyeva O, Christensen DP, Bader L, Vo CT, Wang Y, Rausch DM, Kristensen CK, Gestal-Mato M, In Het Panhuis W, Sjoberg KA, Kernodle S, Petersen JE, Pavlovskyi A, Sandhu M, Moltke I, Jorgensen ME, Albrechtsen A, Grarup N, Babu MM, Rensen PCN, Kooijman S, Seeley RJ, Worthmann A, Heeren J, Pers TH, Hansen T, Gustafsson MBF, Tang-Christensen M, Kilpelainen TO, Myers MG Jr., Kievit P, Schwartz TW, Hansen JB, Gerhart-Hines Z

Nature 2024; 635:987-1000.
PMID: 39537932 doi: 10.1038/s41586-024-08207-0

In Brief: The authors developed selective, long-acting agonists of the Gq-coupled neurokinin 2 receptor (NK2R) and used these in mouse and primate models. Activation of NK2R had dual effects on both suppressing appetite centrally and increasing energy expenditure peripherally.

Comment: The authors focussed on neurokinin 2 receptor (*NK2R*) gene (also known as tachykinin receptor 2 (TACR2)), because they first found robust genetic variant associations with HbA1c at this locus. They shifted their attention to obesity when they found associations between a *NK2R* expression-increasing allele and lower BMI.

Neurokinin A is the endogenous ligand for NK2R, but it has a short half-life and lacks receptor specificity. Therefore, the authors developed longer-acting peptide NK2R agonists (EB001/2), whose half-life was extended by covalently attaching the same 16-carbon fatty acid that prolongs the retention of liraglutide, and with potential for once-weekly administration in humans. In mice, these agonists elicited weight loss by inducing energy expenditure and non-aversive appetite suppression. In diabetic, obese macaques, NK2R activation reduced body weight, blood glucose, triglycerides and cholesterol, and improved insulin resistance.

Most currently available drugs to treat obesity act predominantly by reducing appetite and food intake, rather than increasing energy expenditure, which is the other half of the energy balance equation. Drugs that stimulate energy expenditure, such as thyroid hormone, amphetamines and mitochondrial uncouplers, had been used many decades ago as effective weight loss medications, but they all fell out of favour due to cardiovascular safety issues. Therefore, it is encouraging that NK2R agonists did not affect heart rate. They also spared lean mass and promoted insulin sensitization.

The authors comment that there is a high bar for new weight loss medication, as current and emerging treatments may typically already achieve 20% weight loss. Rather than being a potential new single agent therapy, they predict polyagonism strategies that add NK2R agonism to GLP-1 and GIP may provide the greatest therapeutic opportunity.

15.12. Changes in neurotensin signalling drive hedonic devaluation in obesity

GazitShimoni N, Tose AJ, Seng C, Jin Y, Lukacsovich T, Yang H, Verharen JPH, Liu C, Tanios M, Hu E, Read J, Tang LW, Lim BK, Tian L, Foldy C, Lammel S

Nature 2025; 641:1238-1247.
PMID: 40140571 doi: 10.1038/s41586-025-08748-y

In Brief: This experimental study explored why mice show descreasing interest in a chronic high-fat diet (HFD), over time. They identified a neural circuit mechanism that activates hedonic eating behaviour: neurotensin expression and release in the lateral nucleus accumbens (NAcLat) projecting to the ventral tegmental area (VTA).

Comment: As well eating to satisfy our appetites and induce satiety ('fullness'), we eat many types of food for pleasure. This is one of the reasons why foods that are high in sugars, fat and calories increase risks of overweight and obesity. While the leptin-melanocortin pathway that regulates appetite and satiety is well characterised, the pathway responsible for 'hedonic eating' has been less understood.

The authors provide several lines of evidence for the NAcLat → VTA pathway. Artificial optogenetic stimulation of this pathway increased hedonic feeding in mice on regular diet. By contrast, mice fed on a chronic HFD diet were insensitive to the same stimulation, consistent with their reduced interest in that diet, but this process could be restored by returning them to a regular diet. Optogenetically induced hedonic feeding could also be blocked by neurotensin knockout in the NAcLator neurotensin receptor blockade in the VTA. Conversely, neurotensin overexpression also restored weight gain and hedonic feeding in HFD mice.

Drug targeting of neurotensin signalling specifically in the NAcLat → VTA pathway may be a potential strategy to regulate food intake and support healthy body weights.

15.13. Drug development failure: how GLP-1 development was abandoned in 1990

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PerspectBiol Med 2024; 67:325-336.
PMID: 39247927 https://muse.jhu.edu/pub/1/article/936213

In Brief: This perspective paper discusses the lessons to be learnt from the history of GLP-1 based medication development, which is now a multi-billion dollar effective therapeutic approach, but was abandoned in 1990 despite promising early data.

Comment: The author, Jeffrey Flier, was closely involved in the early development of GLP-1 agonists. In 1987, he cofounded Metabolic Biosystems (MetaBio) and obtained from Joel Habener at Harvard University the exclusive worldwide license to their patents for GLP-1 as a therapy for diabetes. They rapidly obtained major funding from Pfizer in return for exclusive rights to the work, and went on to show that GLP-1 infusion enhanced insulin secretion, slowed gastric emptying and reduced hunger. Sadly, none of that work was ever presented publicly or published. The approach of major pharma companies at that time was to keep such data confidential.

MetaBio did not have sufficient time to answer the next challenge, how to overcome the very short half-life of GLP-1, which is only several minutes. Pfizer terminated support for the programme, concluding that injectable approaches were infeasible and that it would need a trans-nasal or other route of delivery (others would later identify and inhibit the responsible enzyme DPP-4). Furthermore, MetaBio's parent company, CalBio, also decided they could not continue the work due to their need to focus as a small company on another emerging treatment for heart failure.

The success story of GLP-1 agonists is told by Lotte Knudsen at Novo Nordisk (1), which began studying GLP-1 in 1992 and acquired the rights to Habener's patents after MetaBio relinquished them. Their key breakthrough was to attach an acylated fatty acid to GLP-1 to enable binding to albumin to prolong its half-life. Both the successes and failures of drug development provide relevant lessons for today.

Reference

1. Knudsen, L. B. 2019. "Inventing Liraglutide, a Glucagon-Like Peptide-1 Analogue, for the Treatment of Diabetes and Obesity." *ACS Pharmacol Transl Sci* 2 (6): 468–84.

15.14. Screening for food insecurity: US preventive services task force recommendation statement

US Preventive Services Task Force, Nicholson WK, Silverstein M, Wong JB, Chelmow D, Coker TR, Fernandez A, Gibson E, Jaen CR, Krousel-Wood M, Lee S, Rao G, Ruiz JM, Stevermer J, Tsevat J, Underwood SM, Wiehe S
JAMA. 2025;333(15):1333-1339. doi: 10.1001/jama.2025.0879

In Brief: This systematic review by the US Preventive Services Task Force concludes that food security can be accurately assessed in clinical settings, without causing any harms. However, due to insufficient evidence of effective interventions on health outcomes they do not recommend routine screening for food insecurity in primary care settings.

Comment: Surveys in the USA estimated that 13% of households experienced food insecurity in 2022. Similar or even higher figures are emerging in other high-income countries. Poverty is the primary cause of food insecurity, with significant variation by race and ethnicity and, unsurprisingly, food insecurity is associated with adverse health outcomes in both children and adults.

The authors found that screening tools perform well in clinical settings. The 2-item Hunger Vital Sign tool is frequently used and shows sensitivity >95% and specificity >82%. It simply asks:

- During the past 12 months, have you worried about running out of food and not having money to buy more?
- During the past 12 months, have you experienced running out of food and not having money to buy more?

Unfortunately, no identified interventions were effective on any health outcome. Unsuccessful trials have examined: informing families about national and local food-related resources; access to a mobile food pantry; or home delivery of meals (tailored to patients with diabetes).

JAMA allows an interesting publication format, where the authors publish a separate *Viewpoint*, allowing them to express the personal views, free from the constraints of the evidence-based medicine format. They remind us that health outcomes are not determined only by clinical interventions, but are significantly influenced by social and economic conditions. They say "*It would be antithetical to a patient- and family-centered approach to ignore the presence of food insecurity for patients while awaiting more evidence*" (1).

The management of many conditions that we see as Paediatric Endocrinologists are underpinned by dietary advice and support, including Type 1 and Type 2 diabetes, obesity, and inborn errors of metabolism. It would indeed be good practice to show our care by sensitively enquiring about the possible presence and impact of food insecurity.

Reference

1. Tumaini Coker, Michael Silverstein, Michael J Barry, Wanda Nicholson. Navigating the Complexity of Food Insecurity Screening. *JAMA* 2025;333;(15):1293-1294. doi: 10.1001/jama.2024.28194.

15.15. Investigating the impact of trial retractions on the healthcare evidence ecosystem (VITALITY Study I): retrospective cohort study

Xu C, Fan S, Tian Y, Liu F, Furuya-Kanamori L, Clark J, Zhang C, Li S, Lin L, Chu H, Li S, Golder S, Loke Y, Vohra S, Glasziou P, Doi SA, Liu H, The VITALITY Collaborative Research Network

BMJ 2025; 389:e082068.

PMID: 40268307 https://www.bmj.com/content/389/bmj-2024-082068.long

In Brief: This literature-based analysis performed forward citation searching of randomised controlled trials in humans that were retracted for any reason. They identified 1330 retracted trials and 847 systematic reviews that included any retracted trials in a total of 3902 meta-analyses. The authors replicated those meta-analyses but excluding any retracted trials; this changed the direction of the pooled effect in 8.4% (95% CI 6.8% to 10.1%) of meta-analyses, and the statistical significance in 16.0% (14.2% to 17.9%).

Comment: Unfortunately there are increasing numbers of research papers, including randomised controlled trials, that are retracted after publication due to questionable issues in their processes or data quality. Fortunately, you can search for retracted papers in the online Retraction Watch database (https://retractiondatabase.org/), which was established with major philanthropic funding. However, retractions often occur after the published data are included in systematic reviews and subsequently contribute to the evidence base that supports clinical guidance and public health policies. Most of these are not re-evaluated until we are aware that new evidence is available.

The authors caution that incorporation of "contaminated" evidence into clinical practice guidelines may lead to incorrect conclusions and potentially harm patients. A worrying finding was of 157 clinical guidelines that relied on evidence from 69 systematic reviews that were significantly influenced by meta-analyses containing retracted data. Each retracted trial could contaminate, on average up to 13 meta-analyses from 3 systematic reviews, and each systematic review would further contaminateat least 3 clinical guidelines. The authors present some examples of affected guidelines on management of unexplained infertility, postoperative nausea and vomiting and the use of ACE inhibitors.

Addressing this issue will require the attention and active input of health professionals, editors, publishers, organisations and scientific societies to monitor and assess the impact of retracted papers on their evidence and clinical guidelines.

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