Yearbook of Paediatric Endocrinology 2018

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Preface

The Yearbook of Paediatric Endocrinology counts years from June to June, when we submit the manuscripts to our publisher, and so much happened since June 2017.

Our 13 Associate Editors and their coauthors do not take anything for granted and have once again done an enormous work to discern this year's advances. You will see that we cite papers on genomics and genetics, molecular biology and systems biology, evolutionary biology, clinical trials and medical reports to provide new insights in paediatric endocrinology, as the complexity of our field increases.

Among other highlights, the Yearbook 2018 describes: new treatments (MC4R agonist for monogenic obesity; long-term outcomes of rhGH in chronic inflammatory disease; FGF23 antibody in children with XLH; oral GnRH antagonist), new genes (the CLCN2 chloride channel in primary hyperaldosteronism; genetic heterogeneity in T1DM; and new genes in severe obesity and hypogonadotrophic hypogonadism), new mechanisms (Stella insufficiency in oocytes induced by maternal obesity; noncanonical thyroid hormone receptor signalling; epigenetic control of puberty; hypothalamic stem cells control ageing speed; estrogen receptors and excess autoimmune disease in women) and other findings with important implications (consensus definition of fetal growth restriction in newborns; remission of childhood overweight on the risk of T2DM; the 'nocebo' effect; how your Pediatric Department can support Global Health).

A growing number of included papers describe *non-genetic inheritance* (NGI). Transgenerational epigenetic inheritance is the form of NGI that has gained eminence: germline transmission of DNA methylation patterns, histone modification and small RNAs trigger the inheritance of traits, including child growth, puberty and development. But according to a new book by Russell Bonduriansky and Troy Day *Extended Heredity: A New Understanding of Inheritance and Evolution* (Princeton University Press), "Epigenetic inheritance is only the tip of the NGI iceberg." NGI also includes adaptive parental effects, social learning, the inherited microbiome, and structural inheritance in single-celled eukaryotes in predicting adaptive responses.

In this Preface, we annually highlight a prize given in the field of endocrinology. Time and again, metabolic regulation attracts the highest accolades, and we salute Jeffrey Hall, Michael Rosbash, and Michael Young, recipients of the 2017 Nobel Prize for Physiology or Medicine, for their discoveries of molecular mechanisms controlling the biological clock. We also mark each year important science anniversaries: in 1918, L. Greving described the nervous connections between the hypothalamus and pituitary gland – a central dogma of endocrinology. Greving then discovered the tract of unmyelinated nerve fibers running down the neural stalk into the posterior pituitary. But 1918 was also the year of the Spanish flu, killing 50 million people, and World War I ended. Ninety-nine years later it was shown that these hardships in childhood were associated with worse physical and mental health, education, cognitive ability and subjective wellbeing at older ages, and that hardships matter more if experienced in childhood (Havari E & Peracchi F. Growing up in wartime: Evidence from the era of two world wars. *Econ Hum Biol*. 2017;25:9-32).

We thank Chris Kelnar and his team for their contribution over the last six years; his initiatives in evidence based medicine are now firmly embedded throughout the Yearbook. This year we welcome Anne-Simone Parent, who leads a new chapter devoted to *Puberty*, and Olle Söder now devotes his chapter to *Gender Dysphoria and DSD*. We are tremendously grateful to ESPE for their continuing endorsement of the Yearbook series and to BioScientifica for their support. This 2018 edition is the first to be published online only and ***we welcome your feedback*** on whether you wish to receive this in future as: online only, online plus in print, or only in print.

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13. Global Health for the Paediatric Endocrinologist

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Welcome to the 3rd edition of this chapter on Global Health in Pediatric Endocrinology and Diabetes. It is very comforting to witness the rapid increase in high quality research papers that challenge guidelines commonly made for and used in resource-rich settings and that propose new approaches based on the specific characteristics of resource-limited settings. We found many papers on the topic of Developmental Origins of Health and Disease/Type 2 diabetes, on congenital hypothyroidism and on growth/ development and highlight them in three sections of this yearbook chapter.

DOI:10.1530/ey.15.13

How does paediatric endocrinology and diabetes fit in the global initiatives?

13.1 Supporting Global Health at the Pediatric Department Level: Why and How

Pitt MB, Moore MA, John CC, Batra M, Butteris SM, Airewele GE, Suchdev PS, Steinhoff MC on behalf of the American Board of Pediatrics Global Health Task Force

Department of Pediatrics, University of Minnesota Masonic Children's Hospital, Minneapolis, Minnesota, USA

To read the full abstract: *Pediatrics 2017; 139(6)*

This article provides guidelines for leaders in academic institutions in high-income countries who wish to develop a global health stream in their department. We should not forget that over the last 25 years, major changes in our world have decreased the distances between nations. Pediatric residents who train in high income countries are increasingly expressing interests in global health. In our mind, this reflects as much the personal interest of the younger generation in supporting children who live in resource-limited countries as the bidirectional need for such a change. For instance, in pediatric endocrinology, and as illustrated in several other papers in this section, the future generation of pediatric endocrinologists (whether in high-income or in low-income countries) will benefit from the increased knowledge that results from global interaction. The identification of the appropriate laboratory tests to access in resource-limited countries could also generate a healthy reflection on the most appropriate use of often expensive and invasive tests in high-income countries; understanding attitudes towards newborn screening for congenital hypothyroidism or towards the quality of life of children with disorders of sex development in resource-limited settings may help the pediatric resident to optimize the care of immigrant populations in high-income countries; researching the relationship between immune function and growth in children in South America will bring new knowledge that can be applied to our understanding of growth in high-income countries. Finally, we should also not forget that global health does not only apply to children living in resource-limited settings but also to immigrant or indigenous populations living in high-income countries. Their access to medical care is often poor. For instance, in 2017, in Canada, the life expectancy of the Inuit (a group of culturally similar indigenous peoples inhabiting the Arctic regions of Greenland, Canada and Alaska and who were present for several thousands of years prior to the arrival of the first Europeans) was 64 years for men and 73 years for women, respectively; 15 and 10 years lower than for the general population of Canada.

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How does paediatric endocrinology and diabetes fit in the global initiatives?

13.2 Worldwide burden of cancer attributable to disease and high body-mass index: a comparative risk assessment

Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter MJ, Ezzati M
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To read the full abstract: *Lancet Diabetes Endocrinol 2018; 6(2):95-104*

As non-communicable diseases (NCDs) are reaching epidemic levels, emerging data elucidate the devastating non-metabolic long-term risks of overweight, obesity and diabetes. Using published relative risk analysis and cancer incidence estimates from the GLOBOCAN project, the authors provide a thorough risk analysis of site-specific cancers including colorectal, gallbladder, pancreatic, liver, breast, and endometrial cancer attributable to high BMI, diabetes, and the combination of the two. Their estimate that 6% of new cancers are due to the combined effect of high BMI and diabetes is substantial and, more concerningly, is projected to increase by 20-30% over the next 10 years. Interestingly, the attributable cases in women are almost double that of men and account for the majority of the projected increase. There was significant regional variability with regards to cancer specific proportions of total cancer burden as well as PAF of cancer attributable to high BMI, diabetes or both, possibly explained by variations in risk factor prevalence. PAFs in low-and middle-income regions were lower than in most high-income regions, although in the absence of disease registries and reliable ascertainment, both diabetes and cancer epidemiologic data from many low- and middle-income countries should be interpreted with caution. However, even when data inaccuracy is taken into account, it is alarming that the proportion of cancer cases attributable to the increase in prevalence of high BMI and obesity was largest in low- and middle-income countries across sub-Saharan Africa and Asia. Most likely, this reflects the rapidly increasing rates of obesity, diabetes and non-communicable diseases in these regions. Immediate preventive public health measures and care delivery efforts need to be identified and put in place to curb this epidemic and its foreseeable short- and long-term detrimental health consequences.

DOI:10.1530/ey.15.13.2

How does paediatric endocrinology and diabetes fit in the global initiatives?

Sewankambo NK
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13.3 Effects of the Informed Health Choices primary school intervention on the ability of children in Uganda to assess the reliability of claims about treatment effects: a cluster-randomised controlled trial

Nsagni A, Semakula D, Oxman AD, Austvoll-Dahlgren A, Oxman M, Rosenbaum S, Morelli A, Glenton C, Lewin S, Kaseje M, Chalmers I, Fretheim A, Ding Y,

To read the full abstract: *Lancet 2017; 390: 374-88*

See comment on 13.4

DOI:10.1530/ey.15.13.3

How does paediatric endocrinology and diabetes fit in the global initiatives?

13.4 Effects of the Informed Health Choices podcast on the ability of parents of primary school children in Uganda to assess claims about treatment effects: a randomised controlled trial

Semakula D, Nsangi A, Oxman AD, Oxman M, Austvoll-Dahlgren A, Rosenbaum S, Morelli A, Glenton C, Lewin S, Kaseje M, Chalmers I, Fretheim A, Kristoffersen DT, Sewenkambo NK
College of Health Sciences, Makerere University, Kampala, Uganda

To read the full abstract: *Lancet 2017; 390(10092): 389-398*

[Comment on 13.3 & 13.4] Access to quality medical care is often difficult in resource-limited settings and depends upon the collaboration of key stakeholder groups, including global/regional health policymakers, national governments and health system managers, the pharmaceutical industry and trained clinicians and health workers. In addition, patient advocacy groups (parents and children) are expected to play a major role in promoting access to health care. For instance, Caring and Living as Neighbours (CLAN, www.clanchildhealth.org) has identified patient groups as the main driver in advocating for essential medicines availability in resource-limited settings. These groups are the main pillars of their intervention.

In a recently released "Call to Action", "non-communicable diseases" (NCD) Child (http://www.ncdchild.org/) emphasizes the importance of promoting "*health literacy of children, youth and their families to ensure the most effective use of essential medicines and equipment*". In 2 studies, the researchers target young children (pediatric study 13.3) and their parents (adult study 13.4). The pediatric study (13.3) randomized whole schools while the adult study randomized individuals.

The pediatric study (13.3) shows that a simple curriculum taught at school increased knowledge and critical thinking about informed health choices. The curriculum comes as a small book ("The Health Choices Book: learning to think carefully about treatments, a health science book for primary school children") that is used by the classroom teacher to discuss 12 basics concepts around treatment adequacy. Children in classrooms where the curriculum was delivered scored much higher on a knowledge test taken at the end of the intervention, compared to the children who did not receive the intervention.

The adult study (13.4) shows that a podcast on Informed Health Choices increased the ability of parents to assess claims about the effects of treatments. The duration of such effects and whether they translate into changed attitudes towards medicines is unclear. One can also wonder whether health literacy could lead to conflicts with traditional healers who commonly serve as the primary healthcare providers, in particular in rural areas.

DOI:10.1530/ey.15.13.4

How does paediatric endocrinology and diabetes fit in the global initiatives?

13.5 Access to pathology and laboratory medicine services: a crucial gap

Wilson ML, Fleming KA, Kuti MA, Looi LM, Lago N, Ru K
Department of Pathology and Laboratory Services, Denver Health, Denver, CO, USA

To read the full abstract: *Lancet 2018; 391(10133):1927-1938*

See comment on 13.7

DOI:10.1530/ey.15.13.5

How does paediatric endocrinology and diabetes fit in the global initiatives?

13.6 Improving pathology and laboratory medicine in low-income and middle-income countries: roadmap to solutions

Sayed S, Cherniak W, Lawler M, Tan SY, El Sadr W, Wolf N, Silkensen S, Brand N, Looi LM, Pai SA, Wilson ML, Milner D, Flanigan J, Fleming KA

Department of Pathology, Aga Khan University Hospital Nairobi, Nairobi, Kenya

To read the full abstract: *Lancet 2018; 391(10133):1939-1952*

See comment on 13.7

DOI:10.1530/ey.15.13.6

How does paediatric endocrinology and diabetes fit in the global initiatives?

13.7 Delivering modern, high-quality, affordable pathology and laboratory medicine to low-income and middle-income countries: a call to action

Horton S, Sullivan R, Flanigan J, Fleming KA, Kuti MA, Looi LM, Pai SA, Lawler M

School of Public Health and Health Systems, University of Waterloo, Waterloo, ON, Canada

To read the full abstract: *Lancet 2018; 391(10133):1953-1964*

[Comment on 13.5, 13.6 & 13.7] Published just a week before the World Health Organization put out their first Essential Diagnostics List (http://www.who.int/medical_devices/diagnostics/WHO_EDL_2018.pdf), this series of 3 papers highlights the previously often unrecognized but important role of pathology and laboratory medicine (PALM) services in low- and middle-income countries (LMIC). Increasingly, modern medicine relies on diagnostic testing to confirm clinical diagnoses, including through in vitro diagnostics, devices, pathology and radiology procedures – often avoiding morbidity, mortality and a negative economic impact from a wrong diagnosis. Endocrine conditions such as diabetes and lipid metabolism disorders are prime examples that can be difficult to diagnose, classify, treat and monitor based on clinical grounds, especially in their asymptomatic stages. While in high-income countries PALM are used for 2 out of 3 health conditions, LMICs continue to have limited access to PALM services despite bearing a disproportionate share of the global burden of disease with much scarcer access to resources.

The first paper (13.5) outlines key barriers to setting up PALM in LMICs, including a shortage of human resources and workforce capacity, a lack of continuing medical education, an inadequate infrastructure for laboratory services, and absence of standards for rational use of resources, quality, and accreditation. *In the second paper (13.6)*, the case is made for a universal health coverage supported laboratory and health system that is aligned with the Sustainable Development Goals. Avoiding the mistakes of vertical, siloed programs, successes from programs such as PEPFAR should be incorporated, including investment into an improved infrastructure, a solid health care workforce, the wise use of task shifting and task sharing with community health workers, and the value and cost-effectiveness of high quality care along the care delivery cascade. The delivery package proposed aligns with needs for non-communicable disease programs in LMICs (including those suitable for pediatric endocrine services), suggesting evidence based, innovative, locally adapted health care delivery services that incorporate PALM and are integrated into a national health system strategy, conceptualized by local leaders with support from international organizations and stakeholders. *The third paper (13.7)* takes on a political, systems, advocacy and financing perspective to establishing sustainable high-quality PALM services in LMICs. Actionable recommendations are outlined and should be understood as an attempt at not only holding local and international stakeholders responsible for implementing the required services, but also at assuming responsibility among the PALM professionals to take leadership and advocate.

The challenges, potential solutions and proposed political and advocacy strategies for PALM services are fully relevant for global pediatric endocrinology and diabetes. Many parallels exist and several of the outlined suggestions for PALM are immediately applicable to establishing pediatric endocrine services in LMICs. Further, as capacity for pediatric endocrinology in LMICs is increasing through subspecialty training programs such as the Pediatric Endocrinology Training Center for Africa (PETCA) and the Pediatric Endocrinology Education Program for Haiti (PEEP-H), graduates seeking to establish their endocrine practices in their countries will need available, affordable and accessible PALM services to effectively deliver their care. Global efforts to achieve the Sustainable Development Goals need to be leveraged to align national and international stakeholders, move towards universal health coverage, and develop national strategic health care plans that are appropriately resourced to facilitate locally adapted, quality, cost-effective and equitable care – including in subspecialties like endocrinology.

DOI:10.1530/ey.15.13.7

13.8 Developmental Origins of Health and Disease: the relevance to developing nations

Mandy M, Nyirenda M
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To read the full abstract: *Int Health 2018; 10; 66-70*

This article summarizes the concept of Developmental Origins of Health and Disease (DOHaD) and emphasizes its potential relevance to the marked increase in non-communicable diseases, including Type 2 diabetes, observed in low-resource settings. This is an important topic as the DOHaD concept may be a strong contributing factor to the developing Type 2 diabetes epidemic. Geographical differences between the contribution of maternal nutrition, birthweight and postnatal nutrition are not considered in this article but are likely to influence the relevance of the DOHaD concept across regions. For instance, a large part of the clinical knowledge on DOHaD comes from work performed in India, where small for gestational age (SGA) is highly prevalent. Readers interested in this topic should look at the work by Caroline Fall (Southampton, UK) which focuses on the Indian subcontinent and at the publications by the research team of the New Delhi cohort (started in 1969). Whether the determinants specific to India also apply to other parts of the world where SGA (see Lee et al., Lancet Global Health, 1, No. 1, e26–e36, July 2013) and severe underweight in childhood (see article by NCD Risk Factor Collaboration in the "Growth and Development" subsection of this chapter) seem much less prevalent need to be investigated. There may be country-specific solutions to decrease the adverse consequences of poor fetal development.

DOI:10.1530/ey.15.13.8

13.9 Type 2 diabetes in adolescents and young adults

Lascar N, Brown J, Pattison H, Barnett AH, Bailey CL, Bellary S
School of Life and Health Sciences and Aston Research Centre for Healthy Aging, Aston University, Birmingham, UK

To read the full abstract: *Lancet Diabetes Endocrinol 2018; 6:69-80*

The prevalence of T2DM in youth is increasing dramatically worldwide, but the bulk of the increase is expected to take place in Africa, South East Asia and South America. Although genetic factors may seem to be the obvious reason for such geographical differences, a careful analysis of the existing literature suggests that many factors need to be considered: ethnic differences in the genes associated with obesity or with insulin action/secretion have not been clearly identified; the role of intrauterine retardation and postnatal growth that has been well-studied in India may not be as relevant in other settings, the importance of environmental factors; of chronic infections/inflammation and of the nutritional transition may differ from country to country; little data is available on physical activity in youth living in different cultures and the effect of the known differences in the quality of the national healthcare systems on the recognition and management of T2DM remains poorly understood. Understanding the determinants underpinning the expected worldwide increase in the prevalence of T2DM in youth is important as it may lead to country-specific guidelines for the prevention of this public health epidemic that are different from guidelines published in high-income countries where most studies are performed.
This review also raises the important question of access to medicines. Access to insulin is presently insufficient in many low-income countries and could further aggravate the economic consequences of this epidemic.

DOI:10.1530/ey.15.13.9

13.10 Diabetes in sub-Saharan Africa: from clinical care to health policy

Atun R, Davies JI, Gale EAM, Barnighausen T, Beran D, Kengne AP, *et al.*
Harvard TH Chan School of Public Health, Harvard University, Boston, MA, USA

To read the full abstract: *Lancet Diabetes Endocrinol 2017; 5(8):622-667*

The Lancet Diabetes and Endocrinology Commission provides a comprehensive, evidence-based review of diabetes in sub-Saharan Africa, one of the most important emerging diseases and markers of the global epidemic of non-communicable diseases. The authors provide a detailed analysis of the significant knowledge gaps in the global epidemiology and burden of diabetes and its complications in sub-Saharan Africa and emphasize the need to develop local systems to ascertain population representative data. The commission delineates the current health system's barriers adequate diabetes care delivery in the region, concluding that sub-Saharan Africa remains ill equipped in terms of diagnostic and monitoring tools, adequately trained health care professionals, access to essential therapeutics, and availability of guidelines and disease registries. They add an estimate of the economic burden of diabetes, including direct cost to the individual and indirect cost to countries, including the expected tripling in cost until 2030 and the anticipated inability of health systems in the region to assimilate this financial burden.

Strategies to formulate an appropriate health system response are discussed, including the development of service delivery models that are adapted to the reality of low- and middle-income countries and that enable an effective cascade of care from primary prevention to screening, diagnosis, treatment, and long-term care. A decentralized approach that integrates chronic disease care and borrows from successful HIV care delivery models is suggested and should include task shifting from physicians and nurses to community health workers as well as the use of smart information technology. An appropriate medical, social, and political context is required and may be fostered by aligning the health systems response with global targets (such as the Sustainable Development Goals), and by developing a concerted response from national governments, civil society, third party donors and international agencies such as the World Health Organization, the World Bank, the Global Fund, as well as national (USAID) and international (UN based) organizations.

Concerted action and adequate funding by local, national and international stakeholders to develop effective, affordable, and locally adapted responses to the oncoming epidemic of diabetes and non-communicable diseases in low- and middle-income countries is urgently needed.

DOI:10.1530/ey.15.13.10

13.11 Insights from the WHO and National Lists of Essential Medicines: Focus on Pediatric Diabetes Care in Africa

Rowlands A, Ameyaw E, Rutagarama F, Dipsesalema J, Majaliwa ES, Mbogo J, Ogle GD, Chanoine JP
Endocrinology and Diabetes Unit, British Columbia Children's Hospital and University of British Columbia, Vancouver, BC, Canada; Global Pediatric Endocrinology and Diabetes (GPED)

To read the full abstract: *Horm Res Paediatr. 2018; Jul 26:1-1*

As the global burden of non-communicable diseases (NCD) is rising to epidemic levels worldwide, efforts are underway to build capacity for childhood NCDs in low- and middle-income countries (LMICs), including among health care providers in pediatric endocrinology. With increased ability to recognize and diagnose pediatric endocrine conditions in resource-constrained settings, limited access to essential medicines is becoming more palpable. Following their initial assessment of effective translation of the World Health Organization (WHO) Essential Medicines List (EML) to national EMLs in Central America, this second paper by Rowlands et al. focuses on the African continent. While most of the medicines deemed essential in pediatric endocrinology were present on both WHO and national EMLs, not all were – including life-saving medications like fludrocortisone and diazoxide – and only 50% of the medicines included on the author's master list were included. More concerningly but maybe not surprisingly, neither the WHO nor the national EMLs were reliably predictive of access to insulin and glucagon. The authors verified actual availability and affordability of these two most important medicines for diabetes care with pediatric endocrinologists in 5 African countries of variable Gross National Income and found highly variable actual access. A review of aspects of the health systems in these 5 countries that can affect access to medicines, including health care coverage schemes, outreach capacity to remote regions, government supported special programs, and involvement of the private sector and international support programs are among potential factors that may modulate access.
Stakeholders in the public and private sector need to take action to increase transparency of listed and actual availability of essential medicines, and develop evidence-based recommendations for the procurement and reliable disposition of cost-effective essential medicines.

DOI:10.1530/ey.15.13.11

13.12 Clinical profile of diabetes at diagnosis among children and adolescents at an endocrine clinic in Ghana

Ameyaw E, Asafo-Agyei SB, Thavapalan S, Middlehurst AC, Ogle GD
Department of Child Health, Komfo Anokye Teaching Hospital, Kumasi, Ghana; International Diabetes Federation Life for a Child Program, Glebe, NSW, Australia

To read the full abstract: *World J Diabetes 2017; 8(9):429-435*

This is the first paper to describe the clinical presentation and social determinants in youth with diabetes residing and cared for at a single tertiary care center in Ghana that is supported by the International Diabetes Federation's Life for a Child (LFAC) program. As demonstrated by the ability to conduct and publish this study, LFAC not only provides insulin and diabetes supplies for patients, but is also a vehicle for clinical and research capacity building. While the robustness of study data was limited by the absence of important laboratory tests such as electrolytes and blood gas to determine diabetic ketoacidosis (DKA), or C-peptide, pancreatic auto-antibodies, and genetic studies to evaluate diabetes type, the study nonetheless adds valuable information to a very small body of literature on phenotypes and social determinants in youth with diabetes in low-income countries. The authors confirm clinical observations from similar settings including a female predominance, high rates of DKA and infections at diagnosis, a high crude death rate, and increasing apparent diabetes prevalence as clinical care becomes accessible. Unfortunately, data on glycemic control over time did not seem to be available. However, social challenges were identified including low literacy in 1/4 caregivers, absence of schooling in 1/5 youth, inappropriate grade for age in a similar number along with limited school attendance due to diabetes, and poor coping in 1/6 youth. Further investigations are needed to relate the clinical phenotypes and identified social factors to glycemic control and complications, and to develop and evaluate models of diabetes care delivery that are well-adapted to the described population and setting.

DOI:10.1530/ey.15.13.12

13.13 High Rates of Ocular Complications in a Cohort of Haitian Children and Adolescents with Diabetes

Robinson ME, Altenor K, Carpenter C , Bonnell R, Jean-Baptiste E, von Oettingen J

Department of Pediatrics, Division of Endocrinology, McGill Health Centre, Montreal, QC, Canada

To read the full abstract: *Pediatr Diabetes 2018; 19: (6) 1124*

In this cross-sectional study performed in Haiti, the authors found that 18% of the children and adolescents with diabetes had signs of retinopathy and that 16% had a cataract. This prevalence is clearly much higher than reported in young patients with diabetes living in high-income countries. Importantly, ocular complications occurred early in Haitian patients, 4.9 years after diagnosis of diabetes for retinopathy and 3.0 years for cataract. The prevalence of ocular complications increases with duration of diabetes and poor quality of diabetes management. Not unexpectedly, the management of diabetes is suboptimal in Haiti, one of the poorest countries in the world where healthcare resources are very limited. Indeed, mean HbA1c was 9.8%. Prevalence of retinopathy, but not of cataract, increased with longer duration of diabetes. Whether African ancestry, which is characteristic of Haiti, also predisposes to eye complications, is unknown.

The 2014 ISPAD guidelines recommend retinopathy screening “annually from age 10 or at onset of puberty if this is earlier, after 2 to 5 years’ diabetes duration”. In settings such as Haiti where eye complications seem to develop early, these guidelines may need to be revised and a more intensive and earlier assessment of eye complications may be warranted. Although data are currently not available, it is likely that other micro- and macrovascular complications are also more common in Haitian children with Type 1 diabetes. This study supports the need for capacity building in pediatric endocrinology in Haiti, a task that the authors of this article are presently carrying out through the Pediatric Endocrinology Education Program for Haiti (PEEP-H).

DOI:10.1530/ey.15.13.13

13.14 Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis

Wheeler E, Leong A, Liu CT, Hievert MF, Strawbridge R, Podmore C *et al*.
Department of Human Genetics, Wellcome Trust Sanger Institute, Genome Campus, Hinxton, Cambridge, UK

To read the full abstract: *PLoS Med 2017;14(9):e1002383*

This GWAS meta-analysis combined data from five well known ethnically diverse cohorts (Framingham Heart Study, Atherosclerosis Risk in Communities Study, Multiethnic Study of Atherosclerosis, Taiwan-Metabochip Study for Cardiovascular Disease, and Singapore Prospective Study) to evaluate glycemic and erythrocytic genetic variants impacting HbA1c in individuals of European, African American, and East Asians ancestry. The study found new and known glycemic and erythrocytic genetic variants to influence HbA1c and determined that these variants' contribution to T2DM risk is strongly determined by ancestry. The paper thus sheds light on important questions on the differential interpretation of HbA1c based on ethnic background. Genetic glycemic variants, while increasing T2DM risk in Europeans and East Asians, are not associated with increased risk in African Americans. Conversely, genetic erythrocytic variants, in particular the G202A variant in *G6PD,* confer up to 0.8% lower HbA1c values in African Americans, suggesting higher numbers of false negatives on T2DM screening when using the current HbA1c threshold of >6.5%; the optimal threshold to diagnose T2DM in this population is likely lower. This important finding not only underscores the importance to consider genetic determinants in the development, choice and interpretation of screening and diagnostic tests, but also highlights the need to advocate for equitable inclusion of populations of diverse ancestry in biomedical research. A relatively small number of persons of African and Asian ancestry was one of the main limitations of this study, limiting the discovery of new ancestry-specific variants in the very populations in whom questions remain about the interpretation the HbA1c, including about its diagnostic threshold, extrapolation of estimated average glucose, estimation of glycemic control, and complication risk.

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Advances in the Diagnosis and Management of Congenital Hypothyroidism

The five papers included in this section reflect the increasing interest by resource-limited countries in developing such a program but also highlight specific points that need to be considered in countries that embark in this wonderful initiative to make it successful.

13.15 Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial

Gowachirapant S, Jaiswal N, Melse-Boonstra A, Galetti V, Stinca S, Mackenzie I, Thomas S, Thomas T, Winichagoon P, Srinivasan K, Zimmerman MB
Institute of Nutrition, Mahidol University, Nahjon Pathom, Thailand; Division of Human Nutrition, Wageningen University and Research, Wageningen, Netherlands; St John's Research Institute, Bangalore, India; Department of Health Sciences and Technology, Swiss Federal Institute of Technology, Zurich, Switzerland; Hearing Impairment Research Group, Liverpool School of Tropical Medicine, Liverpool, UK

To read the full abstract: *Lancet Diabetes Endocrinol 2017; 5:853-63*

This prospective, randomized trial investigates the benefits of iodine supplementation (200 mcg per day) in pregnant women from Thailand and India on the neurological development of their children. Iodine readily crosses the placenta and is required for the synthesis of thyroid hormones by the fetal thyroid gland. In addition, iodine is actively concentrated by the mammary gland and serves as the sole source of iodine for the breastfed infant. The authors chose a dose of 200 mcg of iodine per day, between the dose propose by the American Thyroid Association and the European Thyroid Association (150 mcg) and the dose proposed by the WHO (250 mcg) for pregnant and lactating women.

The study found no benefit of iodine supplementation during pregnancy on several developmental tests administered to the child at the age of 4-5 years. However, these results need to be interpreted in the context of a population of euthyroid pregnant women with an initial, pre-supplementation urinary iodine excretion (commonly used as a proxy for iodine intake) of ~130 mcg/L, only moderately below the threshold for iodine deficiency. This is much higher than the urinary concentrations associated with severe iodine deficiency (defined as a median urinary iodine concentration of less than 20 mcg/L) and with severe developmental delay in the offspring. In addition, the children in this study were iodine-sufficient at the age of developmental evaluation (4-5 years).

These data should not lead us to conclude that iodine supplementation during pregnancy is not important but rather show that very mild iodine deficiency during pregnancy does not affect neurodevelopment in the child and that supplementation of the pregnant mother with 200 mcg of iodine per day is safe.

DOI:10.1530/ey.15.13.15

Advances in the Diagnosis and Management of Congenital Hypothyroidism

13.16 Incidence of congenital hypothyroidism in China: data from the national newborn screening program, 2013-2015

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To read the full abstract: *J Pediatr Endocrinol Metab 2018; 31(6):601-608*

This article summarizes the findings of likely the largest program of neonatal congenital hypothyroidism (CH) screening in the world. This is a truly impressive effort. The overall incidence of CH was 1/2421, in line with other reports that also observed a relatively high incidence of CH in neonates born in Asia. However, a visual interpretation of Figure 2 suggests that about 1:10,000 neonates had a TSH between 10 and 20 mU/L. Several factors, duly acknowledged by the authors, make it difficult to determine which proportion of these abnormal TSH values were associated with permanent CH and whether all recalled neonates received L-thyroxine therapy, either for a few weeks or long-term.

A modest elevation of the TSH between 3 and 7 days of life (when screening was performed) could be due to several causes. First, although the National Iodine Deficiency Disorders Elimination Program, which was launched in China in 1993, successfully decreased the prevalence of goiter in schoolchildren from 20.4 percent in 1995 to 8.8 percent in 1999, it appears that areas of relative iodine deficiency are still present in costal regions of China. This could account for a high number of mildly elevated TSH observed in this program. Second, immaturity of the hypothalamo-pituitary-thyroid axis is commonly observed in preterm neonates. In 2010, prematurity was estimated to affect 7.8% of all Chinese neonates. Finally, in a Chinese population, heterozygosity for a common TPO gene founder mutation (2268insT) was found to be 16 times more common in infants with transient neonatal hypothyroidism. It will be important to address these questions in order to optimize the cost-effectiveness of this impressive investment by the Chinese Health authorities.

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13.17 Assessment of knowledge, attitudes and practices towards newborn screening for congenital hypothyroidism before and after a health education intervention in pregnant women in a hospital setting in Pakistan

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To read the full abstract: *Int Health 2018; 10(2):100-107*

This article addresses the important issue of acceptance of the congenital screening for congenital hypothyroidism (CH) by the population in general and the families in particular. While it is usually obvious for the health professional that screening for CH is beneficial to the potentially affected neonate, culture, level of education, superstition, poor communication by the authorities and sometimes cost associated with additional care of the neonate are only a few of the factors that play a key role in ensuring acceptance of a screening program.

These authors acknowledge an important limitation of the study, which is that (because of limited funding), information about the relevance and importance of the screening for congenital hypothyroidism was only provided to pregnant mothers. They appropriately suggest that a communication campaign at all levels (government, health professionals, media) should accompany the large-scale implementation of a regional of national program.

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13.18 Worldwide Recall Rate in Newborn Screening Programs for Congenital Hypothyroidism

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Systematic neonatal screening for congenital hypothyroidism (CH) was first proposed by Dr Jean Dussault, a Canadian (adult) endocrinologist, in 1974. It was rapidly implemented in most high-income countries in the late 1970's and 1980's. Ideally, a screening program should be highly sensitive (able to correctly identify affected neonates) and highly specific (able to correctly identify non-affected neonates): the lower the specificity, the higher the recall rate.

Thanks to an increase in capacity building in pediatric endocrinology in many low-income countries and to an increasing global interest in non-communicable diseases (NCDs) such as CH, more regional or national screening programs are being planned. Based on screening programs performed mainly in high income countries, the incidence of permanent CH is estimated to be 1/3000-1/4000. However, the incidence and cause (dysgenesis vs. dyshormonogenesis) of permanent CH varies with ethnic origin. In addition, little is known on the incidence of CH in low income countries where CH screening is not yet available.

Here, Mehran et al. describe that programs recall many unaffected neonates and they summarizes the many factors that affect the recall rate, including differences in laboratory techniques, sample collection (cord blood vs. postnatal), choice of the primary marker (TSH vs. FT4), iodine deficiency or excess, human error and recall cut-off. Defining the cut-off for recall of a program is a key aspect. A high cut-off may not guarantee the recall of ALL neonates affected with permanent CH but may be sufficient to recall the most severely affected neonates who will benefit from L-thyroxine treatment for the successful prevention of mental retardation. A low cut-off value will lead to the recall of many more neonates, including those who present with mildly, permanently elevated TSH concentrations but who are not at risk for cerebral damage. This question needs to be debated when assessing the cost-benefit ratio of a neonatal CH screening.

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Advances in the Diagnosis and Management of Congenital Hypothyroidism

13.19 Newborn Screening Guidelines for Congenital Hypothyroidism in India: Recommendations of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) - Part I: Screening and Confirmation of Diagnosis

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To read the full abstract: *Indian J Pediatr 2018; 85(6):440-447*

In 2017, the population of India was estimated at 1.28 billion. With a birth rate of 19/1000, it means that 24.4 million babies are born each year in India. More than half of the births take place at home, in particular in rural India. Assuming an incidence of 1:2500 for congenital hypothyroidism (CH), close to 10,000 babies are born with CH each year in India. These numbers highlight the enormous challenge of designing and implementing a systematic screening for CH in this vast country.

Our colleagues from the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) should be commended for producing this consensus document that is the first step towards a national screening program for CH. The proposed guidelines take into account specific characteristics of India. First, they suggest that health professionals choose between cord blood screening and postnatal screening (Guthrie card). This is important in a country where many mothers and neonates may not stay close to the hospital long enough to get postnatal screening. Second, they propose that the health professional sends the sample to either a central laboratory, where available, or to a local laboratory. While central laboratories are likely to offer a better overall organization (reflecting the handling of a greater number of samples) and a better quality control, it may be easier and faster to deliver the samples to a local laboratory.

An important characteristic of India is the high number of home deliveries. India would be a perfect candidate for point of care testing of TSH, which consists of measuring TSH at the bedside (home, hospital) using a portable device. However, while in development, the technology of point of care testing of TSH is not yet available. Once it is, it may become the preferred method of testing for countries, such as India, where many babies are delivered at home or where families are difficult to reach.

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Growth and Development

An increasing number of publications focuses on characteristics of growth and development that are specific to children and youth living in resource-limited countries. Some articles offer thought-provoking hypotheses that may change the way we think about the interaction between growth and the environment.

13.20 Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents and adults

NCD Risk Factor Collaboration (NCD-RisC). 1040 collaborators

To read the full abstract: *Lancet 2017; 390(10113):2627-2642*

Over the past 10 years, the prevalence of Type 2 diabetes (T2DM) has increased disproportionately in Africa, South East Asia, the Middle East and the Asia Pacific region. Interestingly, although we need more studies investigating the prevalence of T2DM in Latin America, the prevalence of T2DM in youth living in these countries does not seem to have increased markedly.

This report on the worldwide prevalence of obesity and underweight in youth is an invitation to reflect on the determinants of T2DM in youth in various low- income settings. The association of intrauterine growth retardation and of postnatal obesity is known to be a major risk factor for the development of T2DM in youth. The world map of the prevalence of underweight in children age 5-19 years shows that the Indian sub continent, and, to a smaller extent, South East Asia, the Middle East and Sub Saharan Africa all have a high prevalence of underweight in young children (likely reflecting a mix of pre- and post- natal growth retardation). The prevalence of underweight in Latin America is low. In contrast, the world map of the prevalence of obesity shows a high prevalence in Latin America and in the Middle East, contrasting with a lower prevalence in Africa and in India (although the risk for metabolic syndrome is higher in Indians compared to non-Indians for a similar body mass index, reflecting differences in body composition). These data suggest that the respective roles of obesity and of pre/postnatal growth retardation may differ in various low-income settings, which in turn may call for country-specific public health policies.

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Growth and Development

13.21 Early childhood linear growth faltering in low-income and middle-income countries as a whole-population condition: analysis of 179 Demographic and Health Surveys from 64 countries (1993-2015)

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To read the full abstract: *Lancet Glob Health 2017; 5(12):e1249-e1257*

This paper adds to the understanding of the factors underlying stunting in low-and middle-income countries (LMIC), a phenomenon that is adaptive to undernutrition, and associates with overall poorer health status and unfavorable social determinants of health. Previously thought to be secondary to predominantly individual and household-level factors, this study elegantly demonstrates that stunting in LMICs can primarily be attributed to population-wide community-level factors.

The authors first used statistical modeling to demonstrate how the trends of the HAZ population mean, standard deviation (SD), and 5^{th} and 95^{th} centiles change based on the proportion of the population that is exposed to factors impairing growth. If a trend is driven by only subgroup, the population SD increases, whereas the SD remains steady if the trend occurs across the whole population. The study team then analyzed cross-sectional data from 0-3 year-old children from Demographic and Health Surveys (DHS) in 64 LMIC, including over half in sub-Saharan Africa and none in North America, to assess the trajectory of early childhood HAZ, and evaluate for individual vs. population-driven growth faltering. They demonstrate that the overall mean HAZ declined over time, confirming early childhood growth faltering, and that across regions the HAZ dispersion remained symmetric during the first 3 years of life when growth faltering is most likely to occur, suggesting that the overall mean HAZ decline over time is experienced by children across the entire HAZ z-score spectrum rather than only by a high-risk group such as the extremely stunted.

While the study's limitations include factors inherent to survey-based data, including anthropometric measurement errors and sample heterogeneity, its results supported by consistent multiple well-designed sensitivity analyses. Early childhood stunting in LMIC may be less attributable to different individual genetic, epigenetic and environmental exposures, but rather may be rooted in community-level social and macroeconomic factors. This represents an important public health concern that needs further in-depth study.

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13.22 Evidence for energetic trade-offs between physical activity and childhood growth across the nutritional transition

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To read the full abstract: *Sci Rep 2018; 8(1):369*

The effect of improving socio-economic conditions on growth has been well described in Europe in the 19th and 20th centuries. For instance, in Norway, height increased by 0.3 cm every 10 years between 1830-1875 and then by 0.6 cm every 10 years between 1875-1930. However, the respective roles of nutrition and physical activities has not been clarified.

The authors present their work as an almost pure natural experiment of the role of physical activity on growth in children. Indeed, over 20 years, in a small remote community in South East Mexico, major changes took place, including introduction of mechanised farming, road access to the community and availability of running water. This led to a decrease in physical activity (e.g. less work on the farm) and to an increase in sedentarity (e.g. more time at school) in the children of this community. The authors however acknowledge that calorie intake, which was not measured, likely increased, although nutrition remained largely traditional with little influence of market food. Their main conclusion is that reduced physical activity was associated with greater increases in weight and height. The most likely interpretation was that those calories that are not burned by physical activity become available for growth and for fat deposition. There are however several important points to remember. First, in contrast to populations in high-income countries, overweight and obesity were virtually non-existent in this small Mexican community. Hence, these results may not apply to high-income countries where caloric intake is usually much greater than the minimum required for growth. Second, energetic trade-offs may not be the only explanation for the effect of physical activity on growth. For instance, physical activity also affects body composition, sleep, mental health and, relevant to the pediatric endocrinologist, hormone secretion. Third, the changes observed over 20 years (water, electricity, roads) may have other consequences that indirectly affect growth, such decreased infectious load (see 13.24). Finally, only prepubertal children were studied, so that the effect of physical activity on growth can not be extrapolated to adult height and weight. Nevertheless, this study emphasizes the need for additional studies on the likely multifactorial effects of physical activity on growth.

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13.23 Trade-offs between immune function and childhood growth among Amazonian forager-horticulturalists

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Pediatric endocrinologists have long known that chronic disease, such as severe asthma or inflammatory bowel disease, leads to slower growth and short stature. But it is not always clear whether this is due to the disease (decreased oxygen to the tissues, decreased absorption of calories, infections), to the treatment (corticosteroid exposure) or to a combination of the two. Pediatric endocrinologists also know that optimization of caloric intake and weight is associated with a better prognosis in children with chronic inflammatory diseases.

The provocative hypothesis tested by Urlacher et al. is that low level inflammation, which does not have severe, visible consequences on the child (such as anorexia or decreased physical activity), contributes to stunting. Their study was performed in a population of children living with chronic parasitic infection in a very low resource setting. In this cross-sectional and longitudinal study, they investigated the relationship between levels of C-reactive protein (CRP, a measure of acute immune activity indicating mild, but costly, systemic inflammation over a period of days), IgG (an intermediate-duration measure of adaptive humoral immune function against viruses and bacteria over a period of months) and IgE (a measure of chronic, relatively low-cost, anti-parasitic adaptive immune function over a period of several years), on short-term (1 week) and long-term (20 months) growth. They observed that increased inflammation was associated with slower growth. They also introduced the concept of “trade-off”, meaning that the calories used to develop and maintain the inflammatory response can’t be used for growth. Finally, they observe that this mechanism is mostly relevant to children with insufficient fat reserves, suggesting that better nutrition could alleviate the detrimental effects of chronic inflammation.

The effect of such a mechanism on growth in resource-limited settings is unknown, but chronic, low grade inflammatory response could represent an additional mechanism contributing to stunting and, therefore, to the development of non-communicable diseases (such as Type 2 diabetes). Whether chronic low-grade inflammation in the pregnant mother would also affect fetal growth and contribute to intra uterine growth retardation is another intriguing question.

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13.24 Comparison of Tanner staging of HIV-infected and uninfected girls at the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu, Nigeria

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This cross-sectional case-control study reports that 8 to 18-year-old girls with perinatal HIV infection are less likely to have attained thelarche, menarche and pubarche than healthy peers matched for age and socio-economic status. Girls with perinatal HIV infection were on average over 1.5 years older than healthy girls at the time they reached Tanner II breast development, and there were trends towards reaching menarche 0.5 years later, and Tanner II pubic hair 1.1-year later. Pubarche was earlier than thelarche in both cases and controls, as previously reported in the Nigerian population. Overall, less than half of the girls with perinatal HIV infection had reached thelarche and pubarche, which likely limited the study's power to detect statistically significant differences in the attainment of more advanced pubertal stages. Interestingly, the average ages at thelarche (12.4±1.99 years) and menarche (12.8±1.3 years) in girls with perinatal HIV infection were quite similar, compared to the expected 2 to 2.5 years duration for individual girls to progress from Tanner II to menarche. Rather than implying a later onset but faster paced puberty, this finding may either result from reporting bias, or could suggest that those who reached menarche could represent a sub-group of girls with perinatal HIV infection who undergo normal puberty.

More studies in boys and girls of various ethnic backgrounds are needed to further explore socio-demographic and environmental differences in pubertal development. Longitudinal cohort studies that prospectively document pubertal onset, progression, timing of menarche and their correlation with bone age, as well as HIV control and anti-retroviral use, inflammatory markers and cytokines, and co-infections and co-morbidities are needed to better characterize the relationship between perinatal HIV infection and pubertal development.

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