Yearbook of Paediatric Endocrinology 2019

Editors
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Ze'ev Hochberg

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Yearbook of
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13. Global Health for the Paediatric Endocrinologist

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Preface

Welcome to the 4th edition of this section on Global Health in Pediatric Endocrinology and Diabetes. We again found a vast array of articles that are relevant to the ambitious 2030 Agenda for Sustainable Development adopted in 2015 by all United Nations member states. Pediatric Endocrinology specifically fits with Sustainable Development Goal 3: "Ensure healthy lives and promote well-being for all at all ages", a Goal that focuses on non-communicable diseases (NCDs).

As we are nearing the 100th anniversary of the discovery of insulin by Frederick Banting (and Charles Best) and John MacLeod (and James Collip), articles on diabetes highlight directly or indirectly the need for better access to affordable insulin. While all aspects of pediatric endocrinology are discussed in the 2018-2019 literature, a number of articles focus on disorders of sexual development and on the relationship between nutrition and stunting.

Diabetes

13.1. Effect of Novartis Access on availability and price of non-communicable disease medicines in Kenya: a cluster-randomised controlled trial

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- The authors evaluated the effect of a Novartis programme that provides metformin at a wholesale price of US$1 per month in Kenya.
- This cluster-randomized controlled trial significantly increased the availability of metformin at health facilities, but not at patient households.

The pharmaceutical industry is often blamed for excessive prices of medicines that prevent the people most in need to access them. This interesting trial (funded by Novartis, a manufacturer of metformin) reports the outcomes of the Novartis-Access program, an initiative designed to make essential medicines available at an affordable price. A portfolio of 14 medicines, including metformin, that are prescribed for treatment of non communicable diseases (NCDs) such as hypertension, heart failure, dyslipidaemia, type 2 diabetes, asthma and breast cancer, was made available for purchase by a main distributor to public and non-profit health facilities in Kenya, at a wholesale price of US$1 per treatment per month. Patients with known diabetes treated with metformin could in turn buy the drug at this low price. The results of this Novartis-Access program show that the initiative did increase availability of metformin at the health facility level but not at the patient level.

The reasons for these somewhat disappointing results are discussed in depth by the authors. These included lack of awareness of the program, relatively short duration of the trial (although a longer-term evaluation is planned), the fact that patients had to be previously diagnosed, and delayed registration of the medicines by the Kenyan

Health Authorities. However, industry-led access-to-medicines programmes are one of several important avenues that can be pursued to improve affordable access to essential medicines and outcome evaluation of these initiatives is therefore a key step. Other sustainable avenues include for instance pooled procurement (whereby a large quantity of medicines is bought at a lower price and distributed between several countries), local manufacturing of drugs and easier approval of medicines in order to increase competition between manufacturers and to decrease drug prices (1).

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13.2. Challenges associated with providing diabetes care in humanitarian settings

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- Practical challenges associated with diabetes care in humanitarian contexts in low- and middle- income countries abound.
- In this position paper, the authors articulate the important needs around diabetes care in the context of the 6 building blocks proposed in the WHO Health Systems Framework (1).

Three articles included in this chapter focus on access to insulin, metformin and blood glucose monitoring tools. Managing diabetes in a humanitarian setting markedly differs from care provided in otherwise stable low-resource settings. With more than 400 million people suffering from (mainly Type 2) diabetes, it is not surprising that diabetes, an NCD that has become a priority on the United Nations agenda, is a common cause of health consultations in refugee camps. This important article highlights several practical issues that go well beyond access to insulin and glucose strips. It makes us reflect on specific needs in emergency, high-risk situations and how to address them.

Key questions include: How to integrate diabetes care in general primary healthcare where expertise is usually unavailable? How to ensure self-management in conditions of food insecurity? How to store insulin and other temperature-sensitive medicines when electricity may be discontinued without warning? How to ensure treatment continuity when the unstable political situation may result in medication interruption (lessons learned from experience in HIV and tuberculosis treatment include the use of buffer stocks and runaway packs to help minimise interruption to medication)? Where to find protocols adapted to these particular conditions (Médecins Sans Frontières has developed guidelines to this effect (2)).

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13.3. Levels of type 1 diabetes care in children and adolescents for countries at varying resource levels

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- The quality and availability of pediatric diabetes management varies from setting to setting depending on the available resources.
- In this position paper, the authors propose a 'levels of care' concept with three tiers that stratifies the existing levels of care into minimal care, intermediate care, and comprehensive care.

This article acknowledges the reality: in many low- and middle-income countries (LMICs), diabetes care is suboptimal and is associated with high mortality and morbidity. The authors propose a "Levels of Care" framework for T1D care that can guide health authorities to focus their efforts on appropriate objectives for better diabetes care. This article builds on previous work by the first author who developed a standardized, reproducible Child Program Index of diabetes care measure that can be used to assess critical factors influencing diabetes treatment outcomes (1). Indeed, while we are all familiar with the "gold standard" approach as described in the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines, we do not always appreciate the "next step" approach that will lead to an improvement in diabetes care.

The authors propose nine levels of diabetes care, from a "Minimal care" (characterized by poor insulin access, poor education and uncommon blood glucose testing and associated with elevated HbA1c values and high mortality) to "Intermediate care" (characterized by appropriate access to human insulin and blood glucose strips and associated with low incidence of complications) and "Comprehensive care" (characterized by access to insulin analogs or insulin pumps, multidisciplinary diabetes team and optimal blood glucose monitoring and associated with the lowest HbA1c and prevalence of long term complications). The association between the various components of diabetes care (insulin access, blood glucose monitoring, HbA1c measures, complications screening and quality of diabetes education) and the clinical outcomes (mean HbA1c and prevalence of mortality and complications) at each level of care will serve as a guide for health authorities wishing to implement additional actions for diabetes management and encourage them to reach the next level of care.

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13.4. Why are we failing to address the issue of access to insulin? A national and global perspective

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(Erratum in *Diabetes Care* 2018; 41: 2048. DOI: 10.2337/dc18-er09a)

- Many people currently in need of insulin are unable to access it.
- Unaffordable price of insulin is a major barrier.
- These authors analyse the causes of unsatisfactory access to insulin from a U.S. and global perspective.

This article identifies the various components of a global framework that regulates insulin affordability: the private sector, the government and a plural sector that includes NGOs, academia, research organisations and patient groups. Presently, the private sector has, by far, the greatest influence on insulin cost. One of the reasons

is that 99% of the value and 96% of the volume of the insulin market are controlled by only 3 pharmaceutical companies (Novo Nordisk, Eli Lilly and Sanofi), which contributes to keeping insulin prices high.

The article discusses 2 important points. First, the emergence of biosimilar insulins, which would be expected to increase competition and consequently improve affordability (1). However, those benefits remain to be seen. It is true that an increasing number of smaller pharmaceutical companies are now manufacturing biosimilar insulins (defined as human or analog insulins that are almost identical to a reference product or comparator). However, with a few exceptions, biosimilar insulins have not been successfully evaluated according to the stringent criteria of agencies such as the FDA (USA), PMDA (Japan) or the EMA (Europe). The WHO is presently working on a prequalification process that could contribute to increasing penetration of insulin in more countries. Secondly, they discuss whether the use of analog insulins, which remain more expensive than human insulins, should be promoted in low resource settings. Indeed, there is a concern that high use of analog insulins could contribute to keeping the overall cost of insulin high. The authors feel that the marginal improvement in metabolic control offered by insulin analogs does not justify their higher price. Whether other potential advantages of analog insulins compared to human insulin (such as convenience and decreased risk of hypoglycemia in settings where glucagon is mostly unavailable) is worth the high price remains to be evaluated (2–3).

As health professionals, our primary goal should be to ensure that patients get universal access to at least human insulin.

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13.5. Blood glucose meters and test strips: Global market and challenges to access in low-resource settings

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- Access to blood glucose monitoring is often poor in resource-limited settings.
- The authors analyse the reasons for suboptimal access, with a focus on cost, availability, system accuracy, competitive bidding, technological trends, and non-financial barriers. Urine glucose monitoring is an alternative where there are cost considerations.

Emphasis has been placed mostly on insulin access for the management of Type 1 diabetes in children. However, blood glucose monitoring is a key component of diabetes management and is typically very expensive in resource-limited settings. Looking at 15 low- and middle-income countries, these authors found that the median cost of 2 glucose strips was 1.00 USD, which is more than twice the median cost of daily insulin needs, making blood glucose monitoring unaffordable for the most patients.

This was acknowledged in the 2018 edition of the ISPAD Clinical Practice Guidelines, which now includes a section for diabetes management in resource-limited settings. The guidelines state that “glucose monitoring is very expensive. We recognize that in many countries the cost of these assessments relative to the cost of living may make this technology unavailable… All centers caring for young people with diabetes should urge nations, states, and health care providers to ensure that children and adolescents with diabetes have adequate glucose monitoring supplies” (1).

In 2017, the World Health Organization (WHO) released the first edition of the “Model List of Essential In Vitro Diagnostics” (“essential diagnostics list”, EDL), which is intended “to provide evidence-based guidance to

countries for creating their own lists of essential *in vitro* diagnostic tests" (2). Blood glucose (determined by glucometer) was included in this original list to "diagnose and screen for diabetes and intermediate hyperglycaemia, to diagnose hypoglycaemia". Although the concept of *ongoing* blood glucose monitoring is not clearly spelled out, this is an important first step that highlights for national health authorities the importance of blood glucose determination by glucometer.

The solutions proposed by the authors are similar to those proposed to improve access to insulin. These include preferential pricing for countries with limited resources, regional pooled procurement programs (whereby a larger quantity of strips are bought at a lower price and distributed between countries), and a World Health Organization (WHO) prequalification scheme, whereby affordable meter and strip systems undergo quality assessment procedures with the aim of increasing market competition and, as a consequence, decrease the price of strips.

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Endocrinology: Newborn Screening

13.6. Newborn screening in the developing countries

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- Congenital hypothyroidism is the most cost-effective screened condition.
- Screening for hemoglobinopathies and glucose-6-dehydrogenase deficiency can be cost-effective in sub-Saharan Africa, India and some parts of Asia where there is a high incidence of these diseases.
- Screening for metabolic conditions should be considered in areas of high consanguinity.
- Review article.

This article provides an overview of the various developing newborn screening (NBS) programs around the world. Slow progress is noted in most continents, with low priority given by health authorities for the funding of nationwide programs in low- and middle-income countries. On the positive side, an increasing number of programs are looking for synergies between various diseases to be screened for. At the present time, the NBS programs are being developed according to protocols used in high-income countries. However, specific issues in low- and middle-income countries such as a high percentage of home births, the absence of reliable transportation of the samples and the lack of reference laboratories make the development of point of care testing (at the bedside) techniques desirables. This research is ongoing (including for congenital hypothyroidism) but is not yet available.

13.7. A pilot study on newborn screening for congenital adrenal hyperplasia in Beijing

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- 44,360 neonates were screened for CAH as part of a pilot screening programme in Beijing.
- In this prospective study, a CAH incidence of 1:7393 was found, and the most common 21 OHase mutation was c.293-13C/A > G.

The authors describe the results of a pilot neonatal screening program for congenital adrenal hyperplasia (CAH) in Beijing. Six neonates with CAH were identified (five of them with severe salt wasting), corresponding to an incidence of 1:7393. Although the authors state that this incidence is higher than the national average, this estimate should be taken with caution as the number of patients enrolled in the study was relatively small (n = 44,360), meaning that the 95% confidence interval of the incidence is very large (1:3450 to 1:33,300). This is a reminder that studies assessing incidence for a relatively uncommon disease need to be appropriately powered.

The authors acknowledge two weaknesses of the screening process that illustrate the practical difficulties of developing a newborn screening program for CAH in a country where many families live far from hospitals. First, more than 25% of the neonates with an elevated 17OHP could not be contacted for follow up, meaning that their incidence of CAH may be underestimated (although the majority of those who could not be recalled had relatively lower 17OHP values). Second, the neonates with a positive screening test could be seen in clinic for retesting only within 13 to 83 days after the screening test. As a consequence, all neonates with salt wasting CAH had already presented with severe hyponatremia and hyperkaliemia at the time of diagnosis. The authors of this important work are already working on an improved screening process with a shorter turnaround time, involving faster transportation and processing of the samples.

Endocrinology: Disorders of Sexual Development

13.8. Malaysian females with congenital adrenal hyperplasia: surgical outcomes and attitudes

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- The outcomes of feminizing genitoplasty of 46,XX individuals with CAH were reviewed in this cross-sectional study.
- The study highlights the importance of cultural sensitivities, access to medical treatment and timing of the diagnosis on attitudes toward feminizing genitoplasty in Malaysia.

The authors should be commended for offering an open-minded analysis of genitoplasty outcomes in a large number (n = 59) of female patients with congenital adrenal hyperplasia (CAH) in Malaysia and for discussing their findings in the context of the Malaysian society and culture. We found the comparison of the differences in "shyness/embarrassment" (in the context of decision-making and perception around DSD) between Malay and Western societies highly interesting. In the Malay society, such shyness is called "Malu" and is considered as a

demonstration of respect towards the elders and the elite. It does not have the negative connotation as found in Western societies.

In 3/4 of the cases, genitoplasty was performed by a surgeon trained in DSD repair. Overall, and this is similar to other reports, there was a wide range of outcomes in terms of satisfaction with the cosmetic results (42% were considered as poor) and preferred age for the genitoplasty (half of the parents prefer to have it performed early in life). Interestingly, the authors reported that little attention was given to clitoris preservation until 2006, but, on the positive side, that this has now become an integral part of surgery. Among the 18 participants who were older than 18 years, the authors reported that only one participant was married and only two were sexually active. This very low number is consistent with other reports of poor social outcomes among female CAH patients. However, this has to be interpreted in the context of a progressively older age of marriage among Malaysian women (25.7 years in 2010) (1). Finally, the patient population investigated in this study is quite young and it is very important to obtain long-term follow up data on fertility, sexual satisfaction and overall quality of life.

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13.9. Incidence of disorders of sexual development in neonates in Ghana: prospective study

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- Prospective cohort study of 9255 neonates at a tertiary care center in Ghana to determine the incidence of disorders of sexual development (DSD) using physical examination, ultrasound and 17-hydroxyprogesterone measurements.
- The estimated incidence of a DSD was 28/10,000 live births. Congenital adrenal hyperplasia (CAH) was most common and showed poor survival (3 of 4 identified children died).

Rare endocrine conditions such as DSDs are largely underdiagnosed in settings where the majority of women deliver at home, routine newborn exams are not performed, and health care professionals with expertise in DSDs are not available. As a result, epidemiologic information on DSDs in many low- and middle-income countries is scarce to unavailable, while excess morbidity and premature mortality (such as from CAH) prevail.

This study from Ghana is the first to evaluate the incidence of DSDs in newborns in a sub-Saharan African country. Its relatively large sample size allowed for an informative incidence estimate that suggests DSDs may be relatively frequent in sub-Saharan Africa. Beyond such epidemiologic data, the study teaches several important lessons. First, examination of the newborn genitalia is paramount for the ascertainment of DSDs, and this task can be given to lay health workers if properly trained. Next, a history of consanguinity, also obtainable by lay health workers, should increase the level of alertness for congenital adrenal hyperplasia. Further, when pediatric endocrinologists are available in-country, a clinical examination combined with relatively simple diagnostic tools such as a 17-hydroxyprogesterone, electrolytes, and pelvic ultrasound can provide most patients with a diagnosis (1). Lastly, the study highlights the limitations of care for patients with DSDs in low-resource settings: Lack of access to more sophisticated diagnostic tools such as a karyotype and genetic testing limits diagnostic certainty for a proportion of patients, and lack of essential medicines such as hydrocortisone and fludrocortisone (2) likely underlies the excess mortality in patients with CAH.

As capacity for pediatric endocrinology increases in low- and middle-income countries, more studies such as this one will provide valuable information on global epidemiology and setting-adapted care delivery for patients with DSDs.

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13.10. Women with amenorrhea and men with menstruation: the qualitative experiences of people with disorders of sex development in Nigeria

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- This qualitative study evaluated the physical and emotional experiences of 13 adults living with disorders of sexual development (DSD) at a tertiary care center in Nigeria.
- Diagnosis of DSD is frequently delayed in LMIC resulting in development of ambiguous physical traits and features.

This is one of the first studies to report on patients' experiences of living with a DSD in a West African country where diagnoses are frequently delayed until pubertal development or sexual ambiguity becomes obvious in late adolescence or adulthood, and where a male gender assignment in patients with a 46 XX DSD may be more common. Participants in this study had CAH (n = 6, 3 raised as female, 3 raised as male), androgen insensitivity syndrome (n = 3, all raised female), ovo-testicular DSD (n = 2, both raised male), Mayer-Rokitansky-Kuster-Hauser syndrome (n = 1, raised female) and Turner syndrome (n = 1, raised female).

In this setting where sex education is not routine and lay knowledge about normal female and male puberty is limited, menses is seen as a tell-tale sign of being a "real" or "normal" woman and emerged as the central theme for both female and male participants. In females, the absence of menstruation was mostly experienced as a disappointment and elicited feelings of incompleteness. Women associated amenorrhea to a lack of fertility and, as such, a lack of the ability to function as a woman in society. The six males seemed to fare worse than the females in that onset of menses elicited fear, anxiety, depression, and suicidal ideations. This was linked to perceptions of stigma and fear about social labelling and their fate in society. Positive coping in a minority of women resulted from beliefs, such as God having a special plan for them, or women with amenorrhea being "special", and likened to women in paradise who do not need to menstruate.

The study highlights the high level of distress and stigma experienced by patients with DSDs in Nigeria, a finding that is likely to translate to many other settings. Further research is needed to determine whether increased awareness of DSDs, earlier diagnosis, and improved psychosocial support of patients and families can improve physical, mental and social health outcomes in this population.

13.11. Outcome of feminizing genital reconstruction in female sex assigned disorder of sex development in a low-income country

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- This retrospective review of the surgical and psychosocial outcomes included 25 patients who underwent feminizing genital reconstructive surgery in Nigeria.
- Barriers to optimal care delivery for disorders of sexual development (DSDs) in LMICs include late presentations, inadequate diagnostic and treatment facilities, a social desirability of male sex, stigmatization, and high frequency of late sex reassignment.

Care for DSDs that results in optimal bio-psycho-social health outcomes is difficult to achieve anywhere but presents even greater challenges in LMICs. In settings where lay and health professional awareness of DSDs is low, diagnosis is often delayed, and sex of rearing decided upon regardless of the underlying chromosomal, gonadal and phenotypic sex, sexual function, or prospects of fertility. Rather, religious beliefs, cultural norms and societal pressures may predominate the decision-making process. Further, in the absence of sophisticated diagnostic tools providers need to rely on clinical exam, pelvic ultrasound, and minimal hormonal (17-hydroxyprogesterone) and genetic (Barr body detection) evaluation to make a diagnosis and decide on a care plan.

Diagnoses made as late as during teenage years to young adulthood led to gender reassignment in a striking 10 of 25 patients evaluated here (including 8 of 21 with likely 46 XX DSD due to CAH). However, multi-disciplinary care teams are beginning to emerge, and they are reviewing their practice, using small, but feasible and meaningful research studies to improve the quality of their care and health outcomes for their patients. They conclude that timely evaluation, more adequate diagnostic tools, reliable access to hormone treatments, improvements in timing of surgery and operating technique, as well as gender equality and stigma reduction can help to reduce barriers and improve care outcomes.

Growth and Nutrition

13.12. Exposure to improved nutrition from conception to age 2 years and adult cardiometabolic disease risk: a modelling study

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- Perinatal chronic undernutrition plays a role in adult-onset cardiometabolic disease.
- In this 40-year, longitudinal cohort in Guatemala, protein-energy nutritional supplementation during the first 2 years of life reduced the odds of diabetes but increased the risk of obesity and several obesity-related conditions in adulthood.

The Barker hypothesis proposes that intrauterine growth retardation plays a causal role in the origins of hypertension, coronary heart disease, and non-insulin-dependent diabetes in adulthood. In this study, the Barker hypothesis was tested in an original manner. Forty years ago, a randomized trial tested the effect of a nutritional supplement, made from dry skimmed milk, sugar, and a vegetable protein mixture (protein-rich, 90 kcal per 100 mL]) compared to a low-energy beverage made from sugar and water (all calories from sugar; 33 kcal per 100 mL) on growth during the first 2 years of life in rural Guatemala. Forty years later, the adults who participated to the study as infants were evaluated from a cardiometabolic risk point of view. The authors found that early exposure to a high protein/high calorie diet was associated with a 50% decrease in the risk of diabetes but with a significant increase in BMI, obesity and total and non-HDL cholesterol.

This study is important as it highlights the importance of early nutritional exposure in children (1). Of course, many environmental changes that may affect the results of this study can occur over 40 years but high protein intake in infants has been shown in prospective studies to lead to increased weight gain and higher adiposity in childhood. Recent data (not available when the original study was performed) have led pharmaceutical companies to progressively decrease the protein content of formula to match the lower protein content of breastmilk. Although the quality of the protein (humans vs cow) remains different, this quantitative change may decrease the risk of later obesity in formula-fed infants. This study is also an opportunity to remember that breastfeeding remains the first choice for infant nutrition.

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13.13. Independent and combined effects of improved water, sanitation, and hygiene, and improved complementary feeding, on child stunting and anaemia in rural Zimbabwe: a cluster-randomised trial

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- This cluster-randomised, community-based trial investigates whether the combination of a water, sanitation and hygiene (WASH) intervention and of improved infant and young child feeding (IYCF) intervention improves stunting and anemia in children living in rural Zimbabwe.
- Stunting decreased with IYCF, but WASH had no additional effect. Prevalence of diarrhea was not affected by the intervention.

The WASH intervention aims at improving conditions of water, sanitation, and hygiene. The rationale is that WASH will decrease fecal ingestion and as a consequence improve chronic inflammation and environmental enteric dysfunction (EED), regarded as a major underlying cause of both stunting and anemia. The IYCF intervention provides 20 g/d of Nutributter from 6 to 18 months and promotes optimal use of locally available foods for complementary feeding (1). The IYCF intervention alone increased haemoglobin concentrations, reduced stunting by 21%, reduced anaemia by 24%, and increased weight for height, confirming previous studies. WASH, in contrast with a study in Bangladesh but consistent with other trials, was ineffective either by itself or in combination with IYCF.

The authors discuss the possible reasons for the failure of the WASH intervention. First, although there was a good uptake of WASH at a household level, this was much more modest at the community level. Second, previous research has shown that the intensity of WASH implementation is an important factor, and its intensity may not have been high enough in this trial. We also wonder whether the beneficial effects of breastfeeding (immunoprotection) could have masked the effects of WASH. These children were breastfed exclusively until age 6 months and $>97\%$ were still at least partially breastfed at 18 months. Finally, the authors only report height SD, not height velocities which could show different results, in particular after exclusive breastfeeding stopped. These data are available and will likely be reported in a subsequent paper. Thus, the lack of effect of WASH observed here does not necessarily mean that it is generally ineffective but maybe its implementation needs to be optimized (2).

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13.14. As tall as my peers – similarity in body height between migrants and hosts

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- This literature review evaluated the phenomenon of faster growth, earlier maturation and often taller adult height in migrant youth as compared to their non-migrant relatives.
- The authors propose a new framework to understand growth regulation and determinants of adult height that includes social networks as a growth regulating entity.

Nutrition, social conditions (housing, water, sanitation), economic status, psychosocial health and environmental factors are well-recognized determinants of human growth. This paper provides an anthropological perspective, arguing that social peer group and social status position of dominance or subordination are regulators of growth. They propose a new framework of determinants of adult height whereby nutrition, health and living conditions are merely *prerequisites* of growth, whereas social mechanisms function as *regulators*.

While this hypothesis is not scientifically proven in this paper, the authors carefully review historic and recent data that support it. By examining immigrant populations who moved from low- to high-income settings, the authors show a significant increase in the immigrant population's mean height by as much as 2 S.D.S. (about 10 cm) over the period of one generation. They revisit previously described observations, that colonial populations who moved from high- to low-income settings where they assumed a dominant social status position grew taller than their peers in their country of origin. In the traditional concept of growth regulation, these marked changes in *mean height* are attributed to improved conditions affecting each individual's growth. However, the population's height *distribution* typically remains unchanged, suggesting that social- and community-based growth adjustment rather than individual factors may underlie the increase in mean height.

While the exact physiologic mechanisms that mediate the hypothesized social growth regulation remain elusive and hypothesis driven at best, the data and arguments presented raise the question whether the concept of stature as a social signal may be a missing link in our current model of growth determinants. This shift in conceptualization of growth regulation may be relevant for childhood stunting interventions in low- and middle-income countries (1). Formally testing this hypothesis is a key next step.

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13.15. The obesity transition: stages of the global epidemic

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- This study uses quantitative data from reputable global data sets to demonstrate that the epidemiology of obesity can be framed as a conceptual model of obesity transition.
- A new framework to classify the obesity epidemic is proposed that may assist policy makers and researchers to improve surveillance and develop targeted preventative obesity interventions.

As pediatricians and endocrinologists, we tend to consider the interplay of biological factors such as genetics, epigenetics and the microbiome, and environmental factors such as sociocultural and economic conditions, policies and the built environment as the most important determinants of obesity. While these factors likely account for the varying distribution and intensity of obesity between geographical regions, it remains that obesity has become a global epidemic across populations.

In this paper, akin to the well-known concept of the epidemiological transition, the authors develop the concept of obesity transition whereby populations predictably transition through four distinct phases of obesity over time: In stage 1, obesity is overall low but at around 5% highest in women, greater in adults than in children, and greater in persons of high vs. low socioeconomic status (SES). All very large low-income countries such as India are currently at this stage. In stage 2, the prevalence increases to 25–40% among adults and to around 10% among children, and the gap between sexes and between SES narrows. All countries that were at stage 1 in 1975 (e.g., Mexico) were at stage 2 by 2016. In stage 3, the adult prevalence stalls while childhood obesity increases slightly, however the sex gap closes and there is a reversal in SES differences. Most European and North American countries are at this stage. Stage 4 is a hypothetical stage, yet to be attained by any country, where the obesity prevalence curve flattens in children, such that eventually leaner children enter adulthood, leading to eventual reductions in the prevalence of adult obesity. Trends towards this stage may be seen in some high-SES subpopulations.

This new concept provides the means for future identification of obesity transition stages in any given population, anticipation of obesity risk in subpopulations, and introduction of proactive measures that may attenuate transition. For instance, understanding a potential mismatch between today's high carbohydrate and high calorie diet and the origin of a population (hunter-gatherers with low insulin sensitivity vs farmers with high insulin sensitivity) might help design individual-specific therapeutic approaches (low carbohydrate diets vs low calorie diets) (2). If future research can identify factors that determine the underlying drivers of transition between stages, might populations be able to attain stage 4?

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Micronutrients

13.16. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries

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- This technical report reviews the global prevalence and public health disease burden of vitamin D deficiency.

- Funded by the Bill & Melinda Gates foundation, the working group of content experts from North America and Europe provide a roadmap outlining population-based strategies to improve vitamin D status in low- and middle-income countries (LMICs).

Population representative data on vitamin D status in LMICs are scarce, particularly in youth. Despite predominantly low-quality literature, the available evidence to date suggests that vitamin D deficiency and nutritional rickets may be widespread globally (1), especially in regions where fortification programs do not exist. Most affected are populations residing in Asia, the Middle East, and Africa, as well as immigrants from these regions living in countries at higher latitudes. This report gathers evidence on global prevalence estimates and on functional consequences of vitamin D deficiency, outlines criteria to define vitamin D deficiency as a public health problem and provides an approach to reduce the associated health burden. While there are no surprising or new conclusions with regards to the recommended method to determine vitamin D status (25-OHD measurements), the cut-off to define deficiency (<30 nmol/L), the availability of reliable sources of vitamin D (most foods and UVB radiation are not), or the known consequences of vitamin D deficiency, novelty lies in the clearly outlined roadmap for action to address the global burden.

The suggested approach is a collaborative action between national ministries of health and international organizations. The roadmap starts with an assessment of vitamin D status, whereby the population status is deemed insufficient warranting public health interventions if more than 20% of the populations have 25-OHD levels <30 nmol/L, or in the absence of available 25-OHD data if the prevalence of rickets is $>1\%$. Next, intervention via introduction of mandatory fortification of staple foods and/or supplementation of at-risk subgroups is recommended as appropriate based on the assessment. Options for vehicles for food fortification including dairy products, edible oils, and flour are mentioned. Lastly, monitoring and evaluation processes accompany the roadmap. The report ends with a list of research opportunities that reflect the many knowledge gaps that are still to be filled. Much is still to be learned, but a first step at tackling vitamin D deficiency and its complications in LMICs has been made.

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13.17. Improved micronutrient status and health outcomes in low- and middle-income countries following large-scale fortification: evidence from a systematic review and meta-analysis

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- This systematic review and meta-analysis aimed to determine the impact of large-scale food fortification (LSFF) on health and nutrition outcomes in low- and middle-income countries (LMIC).
- The authors demonstrate that LSFF increases serum micronutrient concentrations including iodine, with a positive impact on functional outcomes such as a 74% reduction in the odds of goiter.

Micronutrient malnutrition is prevalent in LMIC and associated with the global burden of poverty and disease. Iodine deficiency disorders are the most common cause for preventable neurodevelopmental delay. While salt iodization has long been established as an effective strategy to eliminate iodine deficiency and its disorders, according to the most recent 2017 Iodine Global Network score card, 20 countries in the world remain iodine deficient (1).

This systematic review provides real-world evidence that LSFF increases micronutrient concentrations and reduces adverse health outcomes. The significant reductions in iodine deficiency disorders by means of universal salt iodization are highlighted as a success. While this is indeed encouraging, our challenge remains to

eliminate iodine deficiency on a global scale. As much as salt iodization and other LSFF seem like straight forward interventions, as per the WHO/CDC logic model for micronutrient interventions (2), they do require financial and infrastructure resources to be established; policy frameworks, adequate production and supply, quality control, delivery mechanisms, communication and behavior change strategies to run successfully; and adequate program access and coverage to reach the target population. All of these processes are subject to vulnerability, with issues such as poor vehicle choice, challenges with large-scale distribution, and non-adherence to fortification recommendations being common. Recent experience with iodine status re-evaluation in Haiti (unpublished data) and Tanzania, two countries that are still iodine-deficient, highlight that challenges remain in almost every aspect of LSFF such as salt iodization. Thus, while additional research is needed to inform LSFF program priorities and tackle coverage and access issues among the poor and most vulnerable, the study's findings should encourage widespread use of LSFF, an intervention already largely contributing to alleviating micronutrient malnutrition.

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