

Selected Lectures of the Obesity Marathon

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LECT 1

WHEN RISK BEGINS EARLY: OMICS, OBESITY, AND AGING ALONG THE US/MEXICO BORDER

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Cardiometabolic disease (CMD) risk is disproportionately high along the Texas-Mexico border, where the Border Health Research Cohort (BHRC) has studied Mexican American communities since 2004 through the Cameron County Hispanic Cohort and, more recently, the Starr County Health Study, enrolling over 6,000 adults and children with longitudinal clinical, imaging, questionnaire, and multi-omic data. In this population, 51% have obesity, 25% have type 2 diabetes, over 40% have fatty liver disease, and roughly a third are uninsured or living below the poverty level. In BHRC children specifically, we observed an alarming prevalence of obesity and excess adiposity alongside an alarming burden of CMD risk factors: 61% of 423 children had at least one cardiometabolic risk factor, and 12% had three or more. We asked whether CMD's molecular signature is detectable and reversible in childhood, linking 25 CMD phenotypes spanning liver, adipose, vascular, and dysglycemia traits to the circulating proteome in 273 children and adolescents (13.1 ± 2.7 years; 53% female) via 5,420 proteins (Olink Explore HT). Sixteen traits were reduced by PCA/varimax rotation into six latent factors (~77% of variance), summarizing pro-inflammatory adiposity, liver fat/fibrosis, cholesterol, blood pressure, kidney function, and insulin resistance. We identified a protein signature for each factor. In 685 BHRC adults and 28,256 UK Biobank adults, pediatric and adult CMD phenotype-proteome relationships were highly concordant ($R = 0.25-0.69$), encoding biology of beta-cell health, insulin sensitivity, liver homeostasis, inflammation, and cholesterol metabolism. Multi-protein signatures built in children strongly predicted adult outcomes:

proteomic scores forecast adult all-cause mortality, type 2 diabetes, obesity, hypertension, sleep apnea, and liver disease in the UK Biobank, with hazard ratios up to ~2-fold per SD, independent of age, sex, ethnicity, smoking, alcohol, and deprivation. Many pediatric CMD proteins were dynamic with GLP-1 receptor agonist therapy (matched to STEP 1 data) and linked to genetic CMD liability via proteome-wide association studies, suggesting targetable, modifiable profiles from childhood through adulthood. These findings support an early origin of CMD liability embedded in the human proteome, underscoring the value of precision prevention in this at-risk population to forestall metabolic disease long before clinical manifestation. Among the broadest unbiased multi-omic surveys of CMD in children, this multi-cohort work shows that CMD exists on an age continuum, with molecular signals predictive of long-term adult outcomes already measurable, and potentially reversible, in childhood, with direct implications for health equity in an underserved border population and for precision proteomic assessment in children to improve cardiovascular-disease-free longevity.

LECT 2

AAP GUIDELINES AND EPIDEMIOLOGIC LANDSCAPE OF CHILDHOOD OBESITY. BEYOND BMI: MEDICAL-SURGICAL MANAGEMENT

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Childhood obesity continues to affect a growing proportion of children and adolescents and is increasingly recognized as a chronic disease requiring long-term management. Current epidemiologic data indicate that approximately one-fifth of U.S. youth meet criteria for obesity, with severe obesity affecting a smaller but rising subset of patients. Prevalence varies across racial, ethnic, and socioeconomic groups, underscoring the influence of social and environmental determinants on disease risk and health outcomes [1]. Childhood obesity is associated with numerous adverse consequences, including cardiometabolic disorders, type 2 diabetes mellitus, fatty liver disease, sleep-disordered breathing, orthopedic conditions, and psychosocial distress.

Contemporary management strategies have evolved from a focus on prevention alone toward early identification and treatment. The 2023 American Academy of Pediatrics (AAP) *Clinical Practice Guideline* characterizes obesity as a chronic medical condition that warrants comprehensive evaluation and evidence-based intervention [2]. Routine BMI assessment beginning at 2 years of age serves as an initial screening tool, followed by evaluation of comorbid conditions and contributing biological, behavioral, psychological, and environmental factors.

Effective programs integrate dietary counseling, physical activity recommendations, behavioral strategies, and meaningful family engagement.

Anti-obesity medications, including glucagon-like peptide-1 receptor agonists, have demonstrated significant reductions in BMI and favorable effects on cardiometabolic risk profiles. When combined with behavioral interventions, these therapies may enhance treatment effectiveness and improve long-term disease control [2].

For adolescents with severe obesity, metabolic-bariatric procedures like sleeve gastrectomy and Roux-en-Y gastric bypass have shown durable improvements in weight status and obesity-associated comorbidities. Published outcomes suggest meaningful benefits in metabolic health, functional capacity, and quality of life, while maintaining acceptable safety profiles when performed in experienced centers [3].

In summary, the epidemiology of childhood obesity highlights an urgent need for comprehensive management strategies that extend beyond lifestyle counseling alone.

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LECT 3

CARDIOVASCULAR PROBLEMS IN CHILDREN WITH OBESITY

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Childhood obesity is not merely a predictor of later cardiovascular disease; it is a chronic disorder in which cardiovascular injury may begin before adulthood. Excess visceral fat promotes insulin resistance, inflammation, oxidative stress, endothelial dysfunction and neurohormonal activation. It clusters with elevated blood pressure, atherogenic dyslipidemia, impaired glucose metabolism and obstructive sleep apnea.

Asymptomatic children may show arterial stiffness, increased carotid intima-media thickness, greater left ventricular mass, remodeling, and subclinical myocardial dysfunction. In adults, being free at age 50 from hypertension, hyperlipidemia, abnormal weight, diabetes, and smoking corresponds to a life-expectancy advantage exceeding 10 years, supporting primordial prevention [1]. Overt events are rare in childhood, but body mass index, systolic blood pressure, total cholesterol, triglycerides, and smoking measured between 3 and 19 years of age are associated with adult cardiovascular events, especially when they cluster [2].

Assessment should extend beyond body mass index to weight trajectory, obesity severity, family history, sleep-related factors, physical examination and accurate blood pressure measurement. Guidance supports measuring blood pressure at each visit from age 3 in children with overweight or obesity and, from age 10, assessing lipids, glucose metabolism and liver function in those with obesity [3]. Ambulatory monitoring and cardiac investigations should be reserved for suspected hypertension or target-organ involvement.

Management should begin at diagnosis and combine intensive, family-based, multicomponent treatment with care of comorbidities. The diet should follow a Mediterranean-style pattern, based on minimally processed foods and rich in vegetables, fruit, legumes, whole grains, nuts, fish and unsaturated fats. Water should replace soft drinks and other sugar-sweetened beverages; ultra-processed foods, refined carbohydrates, processed meats and excess sodium should be minimized. Physical activity should be increased safely to an average of at least 60 minutes/day of moderate-to-vigorous aerobic exercise, including vigorous and muscle- and bone-strengthening activities at least three days/week. Exercise improves fitness

and cardiometabolic health even with modest BMI change; sedentary time should be reduced. The goal is not weight loss alone, but sustained improvement in cardiometabolic health, quality of life, and long-term cardiovascular trajectory.

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LECT 4

THE EUROPEAN PROJECT BETTER4U ON OBESITY

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Obesity is a chronic and heterogeneous condition shaped by complex interactions among biological, behavioral, environmental and socioeconomic factors. Individuals with similar body mass index (BMI) may therefore differ substantially in their underlying metabolic profile, cardiometabolic risk and response to lifestyle interventions. The Horizon Europe BETTER4U project aims to address this heterogeneity by developing and testing personalized strategies for obesity prevention and management [1, 2]. BETTER4U integrates large-scale population data, multi-omics, causal artificial intelligence, digital monitoring and clinical evaluation. Within Work Package 4 (WP4), we investigated BMI-associated metabolic profiles in 314,767 participants from nine cohorts across six countries, using three targeted metabolomics platforms: Nightingale ¹H-NMR, Biocrates mass spectrometry and Metaboneer NMR. Cohort-level associations were adjusted for age and sex and subsequently combined using random-effects meta-analysis. Sources of methodological and

geographical heterogeneity were also investigated. These findings provide the metabolic background for the BETTER4ALL randomized controlled trial conducted within Work Package 7 (WP7). Higher BMI was associated with a broad adverse metabolic signature characterized by increased triglyceride-rich and remnant lipoproteins, greater ApoB-related particle burden, altered branched-chain and aromatic amino acid metabolism, and higher glycoprotein-related inflammatory signals. Conversely, higher BMI was associated with lower concentrations of large and very large HDL components, ApoA1, glycine, glutamine, choline-related metabolites, phosphatidylcholines and lysophosphatidylcholines. Although several associations were consistent across analytical platforms, their magnitude varied across cohorts and geographical settings, supporting the concept that similar BMI values may be associated with different metabolic risk profiles. WP7 will examine the clinical relevance of this heterogeneity in 1,022 adults with overweight or obesity by comparing a personalized, digitally supported intervention with standard lifestyle counseling. At the University of Cagliari, NMR-based metabolic profiling will be performed at baseline and after six months to investigate metabolic correlates of intervention response. BETTER4U combines metabolic, clinical, behavioral and digital information to improve the characterization of heterogeneity in obesity. WP4 provides population-scale evidence that BMI alone does not fully capture metabolic risk, while WP7 will test whether personalized intervention can translate this biological heterogeneity into clinically meaningful differences in response. This integrated approach may contribute to more precise risk stratification and to the development of personalized strategies for obesity prevention and management.

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LECT 5

OBSESITY IN TWINS

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Twins in medicine and research can be looked at from multiple angles. From the perspective of twins and higher-order multiples, there are questions whether individuals born from a multiple pregnancy differ from singletons. As twins are born earlier on average, their birthweight is lower than that of singletons and because of prenatal crowding, birthweight might be even lower than predicted by gestational age. An important question also is whether twin-singleton differences persist throughout life and to what extent these are reflected in measures of body mass index and obesity. The answer to this question is important for health care professionals and researchers, as well as multiples themselves and their parents. To address this issue, we compared twins to siblings from the same family in a within-family design, thereby correcting for familial confounding. Across multiple domains, there is hardly any evidence for twin-sibling differences except in body composition.

The second area of research in which twins play a major role is genetic epidemiology and behavioral genetics. The classical twin design (CTD) compares the resemblance in monozygotic (MZ) twin pairs to that in dizygotic (DZ) pairs and provides first estimates of heritability. Other applications of twin designs involve studies of discordant twin pairs, for example, in which pairs can be either discordant for an exposure such as early antibiotic use, or discordant for obesity itself. I will give an overview of heritability estimates and compare these with estimates from other study designs and with studies applying the discordant twin design.

Finally, in genetic association studies (GWAS), twins are sometimes excluded from taking part, as is the case for studies aimed at identifying genetic regions for birthweight. I will review one example of such a project that indicates that a similar genetic architecture underlies birthweight in twins and singletons.

LECT 6

METABOLOMICS IN PEDIATRIC OBESITY

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In 2013, we published an editorial on this topic [1]. At that time, PubMed contained only 9 papers, 3 of which were experimental studies. As of September 2026, PubMed listed 646 publications, including 33 clinical trials.

We also published a study on placental metabolomics and maternal obesity. Using metabolomic data alone, without incorporating the women's clinical histories, it was possible to distinguish women with normal weight from those with obesity and, within the latter group, to differentiate women with gestational diabetes from those without it [2].

An analysis of the metabolomics literature points to an important role for myristic acid, particularly in immune tolerance and cell adhesion. Myristic acid is also involved in vascular and coagulation pathways. When present in excess, as may occur in obesity-associated metabolic dysregulation, it disrupts immune tolerance, increases cholesterol levels, and leads to metabolic alterations and impaired immune homeostasis.

Myristic acid occurs naturally at high concentrations in nutmeg. Experimental studies have shown that myristic acid supplementation exacerbates adipose tissue inflammation and systemic insulin resistance in the context of a high-fat diet. Furthermore, clinical studies involving Brazilian adolescents have shown that serum myristic acid levels are negatively correlated with the adiponectin-to-leptin ratio.

Another important topic is the interaction among the host, diet, and gut microbiota. In this regard, we are also carrying out the European BETTER4U project, which will provide an opportunity to investigate the metabolomic profiles of thousands of pediatric and adult participants.

The fundamental question is whether gut dysbiosis is a determining factor in obesity, merely a consequence of it, or whether both are true. Experimental studies support a causal role of the gut microbiota in the development of obesity [3].

In particular, obesity is associated with a decrease in bacterial species that produce short-chain fatty acids (*Bifidobacterium spp.*, *Bacteroides spp.*, *Roseburia*

spp., *Anaerobutyricum spp.*, *Faecalibacterium prausnitzii*, and *Akkermansia muciniphila*) and an increase in TMA/TMAO-producing bacteria (*Bacteroides finegoldi* and *Bacteroides uniformis*).

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LECT 7

LIVER CHANGES IN PEDIATRIC OBESITY: WHAT ROLE FOR ARTIFICIAL INTELLIGENCE?

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease in children, with an estimated global prevalence of up to 7.5%. Its increasing prevalence parallels the rise in pediatric obesity, with MASLD being detected in 30-50% of children with obesity and often remaining clinically silent for many years [1]. Early identification of children at increased risk of developing MASLD is crucial to prevent progression to advanced liver disease. In susceptible children, MASLD may progress from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), ultimately leading to liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The diagnosis of MASLD and MASH in children remains challenging, as the differential diagnostic spectrum differs from that observed in adults.

According to the Barker hypothesis of fetal programming of adult diseases [2], exposure to adverse environmental factors during intrauterine life may exert long-lasting effects on metabolic health, potentially increasing susceptibility to MASLD and MASH later in life.

In this complex scenario, conventional diagnostic approaches remain limited, and a gap still exists between the current understanding of this metabolic disorder and its practical diagnosis. Artificial intelligence (AI) is transforming the diagnostic approach to MASLD/MASH, through the integration of conventional ultrasound imaging with biochemical and clinical variables. AI systems could help pediatricians make an early diagnosis of MASLD/MASH. Advanced machine learning (ML) and deep learning (DL) models have been developed in recent years to predict MASLD based on conventional ultrasound images. Among the proposed approaches, the best-performing radiomics model (XGBoost) and DL model (Mod-MHDNet) achieved the best diagnostic performance, enabling widely available and cost-effective assessment of pediatric hepatic steatosis. These advancements offer a promising practical approach for the early diagnosis of MASLD in children [3].

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LECT 8

REVOLUTIONIZING PREVENTIVE CARE: HOLISTIC AVATAR INTERVENTIONS FOR FAMILY-CENTERED OBESITY PREVENTION

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Childhood obesity represents a major preventive health challenge because its consequences extend

beyond excess weight. Metabolic abnormalities may begin during childhood and persist into adulthood, increasing the risk of hepatic, cardiovascular, and metabolic complications. Metabolic dysfunction-associated steatotic liver disease (MASLD) illustrates this progression and reinforces the importance of education and prevention before established disease develops [1].

Prevention cannot focus on the child alone. Nutrition, physical activity, sleep, and other health behaviors develop within the family environment, where parents and caregivers play a central role. Digital interventions can extend preventive education beyond clinical encounters and have improved selected obesity-related behaviors and outcomes among culturally and linguistically diverse families. However, gaps remain in sustained engagement, accessibility, cultural responsiveness, and meaningful family participation [2].

Our previous work using animated approaches to health communication demonstrated the potential of visual strategies to support health education [3]. Advances in conversational artificial intelligence now create the possibility of moving from one-way educational media toward interactive communication. These considerations guided the development of a holistic conversational avatar prototype for preventive wellness education.

Rather than designing an avatar to interact independently with children, we adopted a family-centered model recognizing parents and caregivers

as central agents of childhood behavior change. The avatar is designed to listen, identify family needs and barriers, personalize educational guidance, and connect families with curated evidence-based resources. Voice, visual communication, multilingual capabilities, and culturally responsive content are incorporated to support accessibility. This approach recognizes that conversational AI involving children requires particular attention to developmental vulnerability, privacy, consent, trust, and adult oversight.

The prototype illustrates a potential evolution of multimodal health education from information delivery toward personalized interaction. Its purpose is not to replace parents or healthcare professionals, but to strengthen the connection among families, reliable health information, and preventive care. Future research should evaluate safety, acceptability, engagement, comprehension, cultural responsiveness, family behavior change, and ultimately its potential contribution to obesity prevention.

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