BIOGRAPHICAL SKETCH

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NAME: Caprio, Sonia

eRA COMMONS USER NAME (credential, e.g., agency login): CAPRIO

POSITION TITLE: Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Universita di Medicine e Chirurgia, Naples, Italy	M.D.	07/78	Medicine
Universita di Medicina e Chirurgia, Naples, Italy	Residency	12/80	Internal Medicine
Temple University Hospital, Philadelphia, PA	Research Fellow	01/81- 12/83	Internal Medicine

A. Personal Statement

I have been involved in patient-oriented research in the field of Childhood Obesity and Type 2 diabetes (T2D) in youth for the past 25 years. Realizing the need to understand the pathophysiology of T2D in Obese Youth I have been investigating the role of insulin resistance and beta cell dysfunction at the earliest stage of T2D, namely Impaired Glucose Tolerance. My research in pre-diabetes in obese children and adolescents has brought into focus at the national level the magnitude of the obesity problem in children in the US. This research demonstrated a much faster tempo of progression of beta cell failure in obese adolescents, which helped to stimulate the funding of two NIDDK RCT in obese youth; The TODAY and RISE studies that are currently in progress. In recognition of the importance of this work in 2008 Dr. Caprio was awarded the prestigious *"Distinguished Clinical Scientist Award (DCSA)" from the American Diabetes Association.* This research spans both clinical and basic research in metabolism, genetics, neuroscience and imaging and has been recognized by receipt of *the "Distinguished Leader in Insulin Resistance" 2015 Award* from the International Committee for Insulin Resistance (ICIR). *More recently, I have been awarded the 2017, Samuel Fomon Award in Nutrition from APA*.I also bring to the program ongoing collaborations with international experts in genetics of T2D (Dr. Leif Groop) and physiology and use of complex mathematical models for the analysis of beta-cell function (Dr. Claudio Cobelli). Over the past few years, our group has assembled a large multiethnic cohort of children/adolescents (n=1100) and genotyped them for relevant gene variants found to be associated with T2D in adults from the GWAs. Our current and future approach is to capitalize on our clinical and translational research arena to recruit subjects from this cohort with specific genotypes of interest (such as the *TCF7L2* snp) and to perform hypothesis-driven phenotyping to elucidate underlying mechanisms whereby gene variants exert their effects during adolescence, a critical time for youth onset T2D.

Landmark Publications:

a. Caprio S, LD Hyman, C Limb, S McCarthy, R Lange, RS Sherwin, G Shulman, WV Tamborlane. Central adiposity and its metabolic correlates in obese adolescent girls. *Am J Physiol* 269 (Endocrinol Metab 32):E118-126, 1995.
b. Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, Savoye M, Rieger V, Taksali S, Barbetta G, Sherwin RS, Caprio S. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 346(11):802-810, 2002.
c. Weiss R, Dufour S, Taksali SE, Tamborlane WV, Petersen KF, Bonadonna RC, Boselli L, Barbetta G, Allen K, Rife F, Savoye M, Dziura J, Sherwin R, Shulman GI, Caprio S. Pre-type 2 diabetes in obese youth: A syndrome of impaired glucose tolerance, severe insulin resistance and altered myocellular and abdominal fat partitioning. *The Lancet.* 362:951-57, 2003.
d. Weiss R., Dziura J, Burgert T, Tamborlane W, Taksali S, Yeckel C, Allen K, Lopes M, Savoye M, Morrison J, Sherwin R, Caprio S. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 350:2362-2374, 2004

B. Positions and Honors

Positions and Employment

1986-1989	Postdoctoral Fellow, Pediatric Endocrinology, Yale University, New Haven, CT
1989-1991	Associate Research Scientist, Pediatric Endocrinology, Yale University, New Haven, CT
1991-1996	Research Scientist, Pediatric Endocrinology, Yale University, New Haven, CT
1996-2004	Associate Professor, Pediatric Endocrinology, Yale University, New Haven, CT
2004-Present	Professor, Pediatric Endocrinology, Yale University, New Haven, CT

Other Experience and Professional Services

2003-2007	Member of the Diabetes and Endocrinology and Metabolism study section of NIDDK
2004-Present	Ad Hoc reviewer of the Integrative and Physiology of obesity and diabetes (IPOD) study section , NIDDK
2005-2008	Member of the Food and Drug Advisory (FDA) Committee for Endocrinology and Metabolism
2009-2013	Member of the Clinical and Integrative Diabetes and Obesity (CIDO) study section
2011	Chairperson for Study Section on Molecular Mechanism of Adverse Metabolic Drug ZHD1DSR-K, March 2011
2013	CHAIR, Special Emphasis Panel ZDK1 GRB-J03 “The Microbiome in Child Health, Development and Obesity,” June 2013
2013-2014	Member of the Food and Drug Advisory (FDA) Committee for Nonprescription Drugs Advisory Committee
2013-2016	Member of the American Diabetes Association Clinical Study Section
2013-2016	Member Of the Yale Award Committee
2013-2015	Member of the PEDIATRICS (CHHD-A) Review committee at NICHD

Honors

1987-1989	Juvenile Diabetes Foundation International Postdoctoral Fellowship
1989-1992	*Career Development Award*, Juvenile Diabetes Foundation
2001-2011	K24 *Investigator Award in Patient Oriented Research*
2003	*Bayer Scholar Award in Diabetes Research*
2008-2012	*Distinguished Clinical Scientist Award*, American Diabetes Association
2015	*Distinguished Leader in Insulin Resistance Award*, International Committee for Insulin Resistance (ICIR)
2017	*Samuel Fomon Award in Nutrition from APA*

C. Contribution to Science

1. Metabolic and Imaging studies in children and adolescents. An important feature that distinguishes my research has been the use of sophisticated but relatively non-invasive techniques to evaluate novel pathophysiological questions in scientifically rigorous protocols across all age groups. Using state-of-the-art techniques, such as euglycemic and hyperglycemic clamps, stable isotope dilution methods, indirect calorimetry, microdialysis, magnetic resonance imaging, and more recently ^{1}H-NMR spectroscopy, we showed: the critical role of visceral obesity in adolescents with obesity; the diurnal variations in circulating leptin levels and the ability of selective catecholamine agonists to stimulate lipolysis in subcutaneous adipose tissue. To determine the lipid composition of the muscle tissue and its relationship to whole-body insulin sensitivity, we used for the first time in children ^{1}H-NMR spectroscopy in obese and non-obese adolescents. This study suggested that, early in childhood obesity, abnormalities in insulin action may arise as a result of an over-accumulation of lipid in skeletal tissue independently of total body fat mass. These studies have provided seminal information on the impact of obesity on glucose and lipid metabolism in youth.

   Landmark Publications:

   a. Caprio S, WV Tamborlane, D Silver, C Robinson, R Leibel, S McCarthy, A Grozman, A Belous, D Maggs, R Sherwin. Hyperleptinemia: an early manifestation of juvenile obesity: relations to body fat depots and insulin concentration. *Am J Physiol* 271:E636-E630, 1996. PMID: 8843759
   b. Robinson C, WV Tamborlane, D Maggs, S Enokkson, RS Sherwin, G Shulman, S Caprio. Effect of insulin on glycerol production in obese adolescents. *Am J Physiol* 274:E737-743, 1998. PMID: 9575836

c. Enoksson S, Talbot M, Rife F, Tamborlane WV, Sherwin RS, Caprio S. Impaired in vivo stimulation of lipolysis in adipose tissue by selected β_2-adrenergic agonist in obese adolescent girls. *Diabetes* 49:2149-2153, 2000. PMID: 11118019
d. Sinha R, Dufour S, Petersen K, Lebon J, Enoksson S, Ma YZ, Savoye M, Rothman D, Shulman G, Caprio S. Assessment of skeletal muscle triglyceride content by ^{1}H-NMR in lean and obese adolescents. *Diabetes* 51: 1022-1027, 2002. PMID:11916921

2. <u>*Pathophysiogy of T2D in obese adolescents*</u>.*The unabated rise in the prevalence of childhood obesity has brought out an unprecedented phenomenon rarely seen in pediatrics before: Type 2 diabetes. Prior to our project, little was known about this metabolic state in pediatrics. Although severe obesity has a prominent role in the pathogenesis of T2D in youth, it was unknown whether it is a risk factor for IGT. First, we undertook a study to determine the prevalence of IGT in a multiethnic cohort of obese children and adolescents. Using a clinic-based population cohort of obese youth, IGT was detected in 25% of the obese children and 21% of the obese adolescents, and silent T2D was identified in 4% of the obese adolescents.* Importantly, using the Oral Minimal Model, we found in obese adolescents *pre–existing defects in beta cell secretion* before the transition from normal to Impaired Glucose Tolerance (IGT). This study indicated that the transition to IGT is paralleled by profound decreases in a) insulin resistance, b) beta cell glucose responsivity and c) Disposition Index. This work has laid the foundation for the design of two national multicenter clinical trials funded by NIDDK: The TODAY Study and The RISE Study.

Landmark Publications:

a. Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, Savoye M, Rieger V, Taksali S, Barbetta G, Sherwin RS, Caprio S. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med 346* (11):802-810, 2002. PMID: 11893791
b. Weiss R, Dufour S, Taksali SE, Tamborlane WV, Petersen KF, Bonadonna RC, Boselli L, Barbetta G, Allen K, Rife F, Savoye M, Dziura J, Sherwin R, Shulman GI, Caprio S. Pre-type 2 diabetes in obese youth: A syndrome of impaired glucose tolerance, severe insulin resistance and altered myocellular and abdominal fat partitioning. *The Lancet*. 362:951-57, 2003. PMID: 14511928
c. Weiss R, Caprio S, Trombetta M, Taksali SE, Tamborlane WV, Bonadonna R. Beta-cell function across the spectrum of glucose tolerance in obese youth. *Diabetes* 54(6):1735-43, 2005. PMID: 15919795
d. Giannini C, Weiss R, Cali A, Bonadonna R, Santoro N, Pierpont B, Shaw M, Caprio S. Evidence for early defects in insulin sensitivity and secretion before the onset of glucose dysregulation in obese youths: a longitudinal study. *Diabetes*. 2012 61(3):606-14. PMID:22315322

3. <u>Fat partitioning and insulin resistance in obese adolescents</u>. Altered partitioning of fat, more than overall obesity per se, during adolescence carries a high risk for insulin resistance (IR) and T2D. We described a distinct “endophenotype” in obese adolescents characterized by a thin superficial layer of abdominal subcutaneous adipose tissue (SAT), increased visceral AT (VAT), fatty liver and marked IR. Subsequently, we began to unravel the cellular/molecular mechanisms associated with this phenotype and its relations to IR by combining metabolic/imaging studies with measurements of adipocyte cellularity and transcription of genes regulating lipogenesis/adipogenesis and inflammation. The following key findings emerged: first, the transcriptional signature of the abd SAT in obese adolescents with a High VAT/SAT ratio is suggestive of a low storage capacity which contributes to fatty liver and IR; second, early in the development of T2D in youth, ChREBPβ expression in abd SAT predicts IR, Third, hepatic fat, independent of VAT, is a key determinant of IR, and fourth, SIRT1 gene expression is inversely related to macrophage infiltration in abd SAT.

Landmark publications

a. Taksali S, Caprio S, Dziura J, Dufour S, Cali AMG, Goodman T, Papademetris X, Burgert T, Pierpont, B, Savoye M, Shaw M, Seyal A, Weiss R. High visceral and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic syndrome. Diabetes 57:367-371, 2008. PMID: 17977954
b. Kursawe R, Eszlinger M, Narayan D, Liu T, Bazuine M, Cali AM, Adamo ED, Shaw M, Pierpont BM, Shulman GI, Cushman SW, Sherman A, Caprio S. Cellularity and adipogenic profile of the

abdominal subcutaneous adipose tissue from obese adolescents: association with insulin resistance and hepatic steatosis. Diabetes 59:2288–2296, 2010. PMID: 20805387.

c. Kursawe R, Caprio S, Giannini C, Narayan D, Lin A, D'Adamo E, Shaw M, Pierpont B, Cushman SW, Shulman GI. Decreased transcription of ChREBP-α/β isoforms in abdominal subcutaneous adipose tissue of obese adolescents with prediabetes or early type 2 diabetes: associations with insulin resistance and hyperglycemia. Diabetes. 2013 Mar; 62(3):837-44. PMID: 23209190

d. Perry RJ, Camporez JP, Kursawe R, Titchenell PM, Zhang D, Perry CJ, Jurczak MJ, Abudukadier A, Han MS, Zhang XM, Ruan HB, Yang X, Caprio S, Kaech SM, Sul HS, Birnbaum MJ, Davis RJ, Cline GW, Petersen KF, Shulman GI. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. Cell. 2015 Feb 12; 160(4):745-58PMID: 25662011

4. Pediatric Fatty liver. Non-Alcoholic Fatty Liver Disease (NAFLD) is becoming the most common cause of chronic liver disease in the western world, in part because of the unabated rise in obesity. Its prevalence is estimated to be 38% among obese children. Two-thirds of children with NAFLD have evidence of nonalcoholic steatohepatitis (NASH) on liver biopsy and are at risk for cirrhosis. Longitudinal studies of NAFLD suggest that the disease may progress more rapidly in children than in adults. In an effort to unravel the pathogenesis and genetic underpinnings of NAFLD in children, we established the "Yale Pediatric NAFLD Cohort", a multiethnic group of obese children and adolescents that is extensively phenotyped with respect to quantification of hepatic fat content and abdominal fat distribution and several pathophysiologic indices, including fasting lipid and lipoprotein profile, glucose homeostasis (OGTT, insulin sensitivity and secretion indices) and 24hr dietary intake. Using this cohort we have been determining the genetic markers and their interaction with macronutrient composition of the diet on their ability to convey susceptibility to NAFLD in obese youth, Furthermore, potential mechanisms that might contribute to the accumulation of hepatic triglyceride accumulation are being assessed for the first time assessed by genotype.

Landmark publications

a. Santoro N, Kursawe R, D'Adamo E, Dykas DJ, Zhang CK, Bale AE, Calí AM, Narayan D, Shaw MM, Pierpont B, Savoye M, Lartaud D, Eldrich S, Cushman SW, Zhao H, Shulman GI, Caprio S. A common variant in the patatin-like phospholipase 3 gene (PNPLA3) is associated with fatty liver disease in obese children and adolescents. *Hepatology*. 2010 Oct; 52(4):1281-90. PMID: 20803499

b. Santoro N, Zhang CK, Zhao H, Pakstis AJ, Kim G, Kursawe R, Dykas DJ, Bale AE, Giannini C, Pierpont B, Shaw MM, Groop L, Caprio S. Variant in the glucokinase regulatory protein (GCKR) gene is associated with fatty liver in obese children and adolescents. *Hepatology*. 2012 Mar; 55(3):781-9. PMID: 22105854

c. Santoro N, Feldstein AE, Enoksson E, Pierpont B, Kursawe R, Kim G, Caprio S. The association between hepatic fat content and liver injury in obese children and adolescents: effects of ethnicity, insulin resistance, and common gene variants. *Diabetes Care.* 2013 May; 36(5):1353-60. PMID: 23275357

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/sonia.caprio.1/bibliography/41141524/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01-HD028016 Caprio 03/01/2015 - 02/29/2020
NIH/NICHD
Metabolic Markers and Predictors of Childhood Obesity
This is a grant started in 1991 aimed at understanding the mechanisms responsible for the insulin resistance associated with childhood obesity.
Role: PI

U01-DK094467 Caprio 07/01/2017 - 07/30/2018
(*NCE)
NIH
Beta-cell rescue in youth with new onset T2DM
The goal of the study is to determine if early intensive insulin therapy in youth with newly diagnosed T2D, by rapidly decreasing fasting and postprandial hyperglycemia (glucotoxicity) will have favorable outcomes on recovery and maintenance of B-cell function (first phase insulin secretion) and long-term glycemic control, compared with treatment with metformin. This is a multi-center study.
Role (Co-PI)

U01-DK099164 Craft 09/01/2016 - 08/31/2018
NIH
Beta-cell Function and Cognition in the Restoring Insulin Secretion (RISE) Study
The goal of the study is to will examine the effects of treatment with metformin or metformin plus glargine on cognitive function and plasma ß-amyloid (a biomarker of cognitive decline related to Alzheimer's disease) in adolescents with prediabetes or early Type 2 Diabetes Mellitus (T2DM) who are participants in the Restoring Insulin Secretion (RISE) Pediatric Study. The ancillary study will also examine whether therapeutic modulation of ß-cell function, insulin sensitivity, and hyperglycemia predicts change in cognition and ß-amyloid.
Role (Co-PI)

U01-DK61230 Caprio sub#11-D19 05/01/2016 – 04/31/2021
NIH/NIDDK/GWU
Today2 Phase 2 (T2P2): Long-Term Post-Intervention Follow-up
The goals of this project are to examine the occurrence and progression of microvascular, macrovascular, and neuropathic complications as well as the psychosocial complications in the young cohort of patients with type 2 diabetes.
Role: PI

1R01DK111038-01A1 (Caprio) 09/22/2016 - 08/31/2021
NIDDKD / NIH
Pathogenesis of Youth Onset Pre Diabetes and Type 2 Diabetes
The goals of this project will be to determine if genetic factors are associated with defects in insulin secretion and incretin system and hepatic insulin resistance in obese adolescents. Our long-term goal is to generate information on both the genetics as well as the pathophysiology of Type 2 diabetes in youth.

R01 DK114169 (Small) 01/01/2018 - 12/31/2023
Neurocognition in Youth with Prediabetes
The major goals of this study are to follow obese adolescents with NGT and IGT from the PYOD Cohort longitudinally in order to determine the changes in glucose tolerance status as well as insulin resistance.
Role: Co-Investigator

5K12DK094714-07 (Tamborlane) 07/01/2016 - 06/30/2021
NIDDK / NIH
Pediatric Endocrine / Diabetes Physician Scientists
The Yale K12 Program is seeking to continue its efforts to address the marked shortage of young pediatric endocrinologists who are trained and have the skills to develop into the next generation of outstanding independent investigators in pediatric diabetes research.

Completed:

R01-HD040787 Caprio 06/01/2010 - 05/31/2015
NIH/NICHD
Pathophysiology of Type 2 Diabetes in Youth
The main objective of this study is to determine the role of insulin resistance and β-cell function in the early stages of impaired glucose tolerance and type 2 diabetes in youth.
Role: PI