Nature and Nurture: Navigating Risk and Treatment for Type II Diabetes and Hyperinsulinemia

Timothy Ryan Smith, MD

Progress in Pediatrics

10/5/18

Disclosures

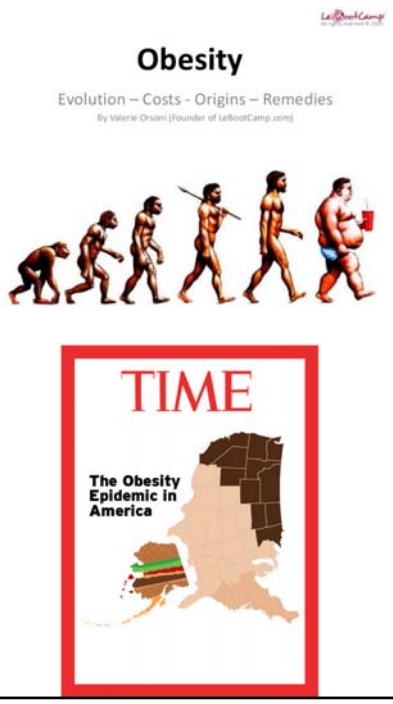
- I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity
- I will review literature for use of metformin in obese children

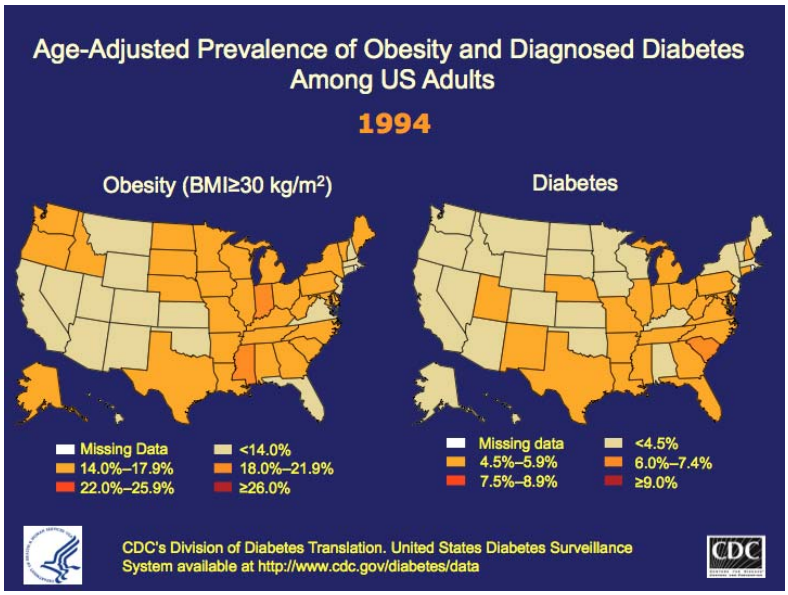
Objectives

- Familiarize yourself with screening for type II diabetes and metabolic syndrome in obese and overweight patient as well as the general population
- Understand the indications for metformin and endocrine referral for children with hyperinsulinemia and type II diabetes
- Appreciate the importance of and tools for motivational interviewing in obese and overweight patients

Frontline of an Epidemic

- Prevalence
- Complications
- Risk factors
- Evaluation
- Management

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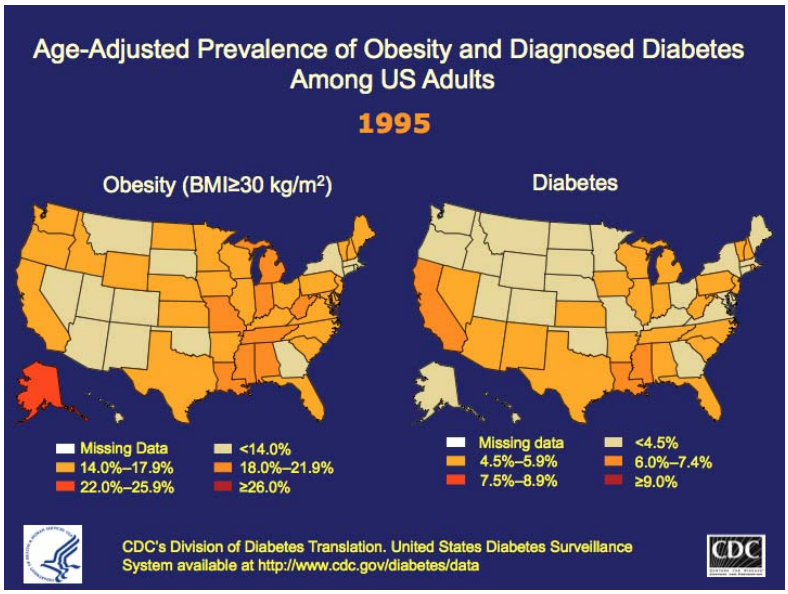
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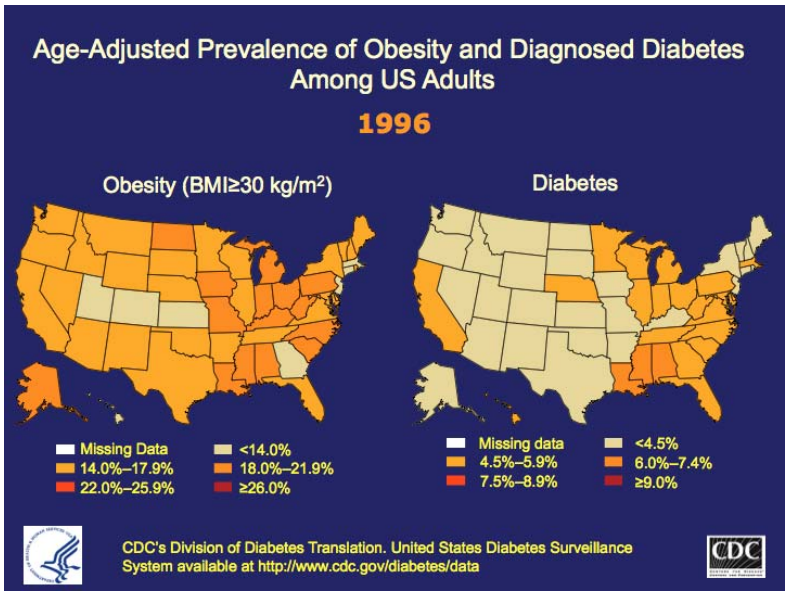
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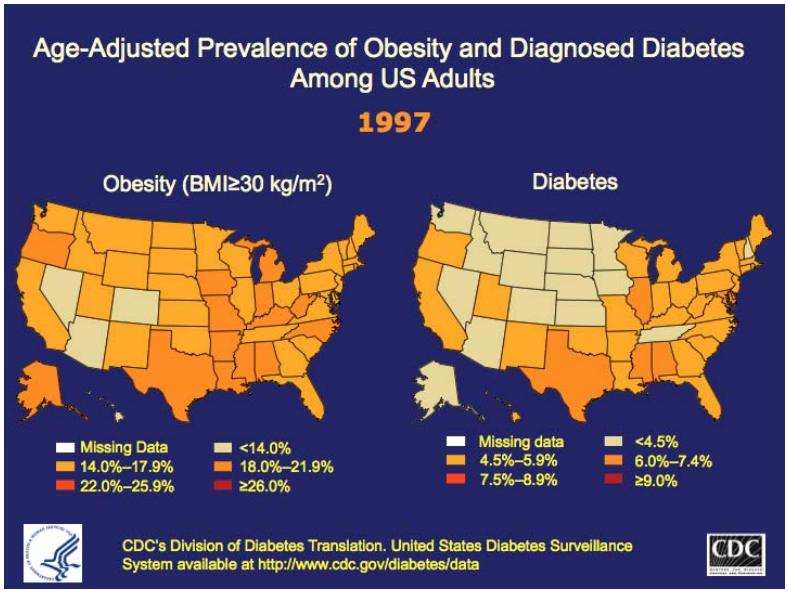
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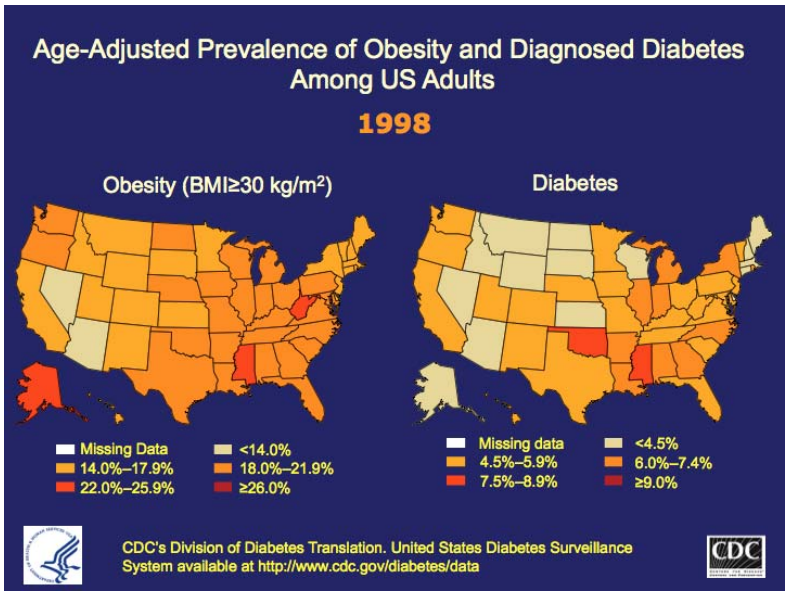
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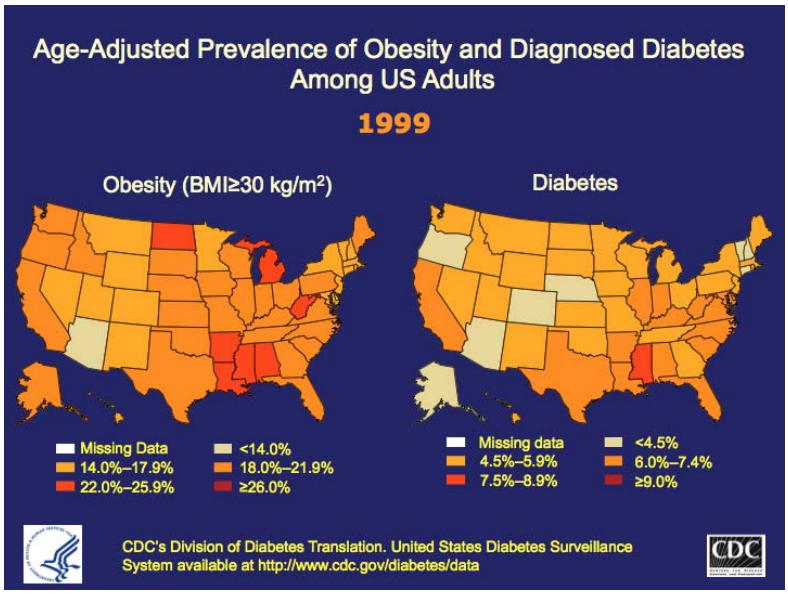
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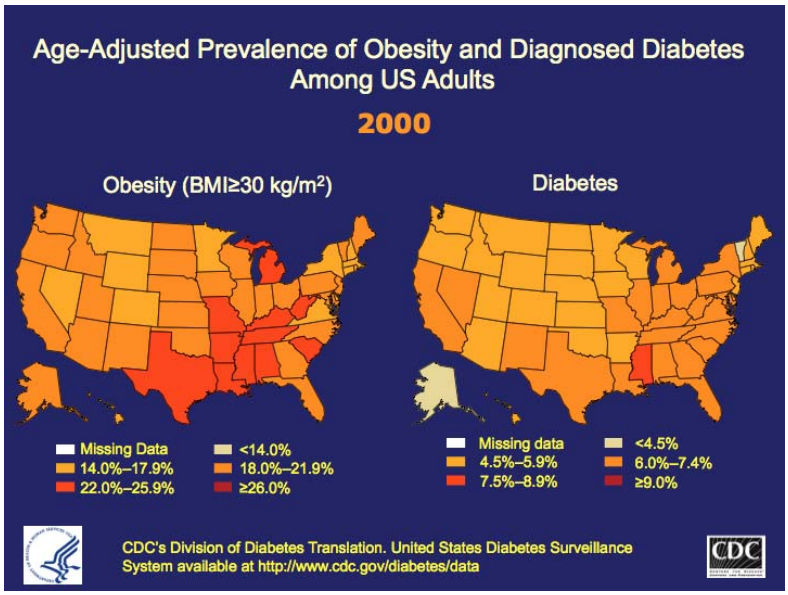
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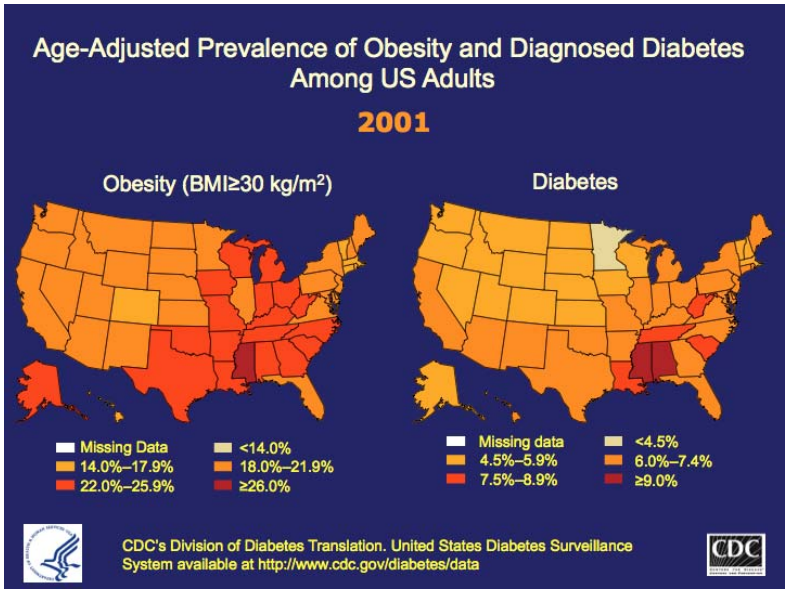
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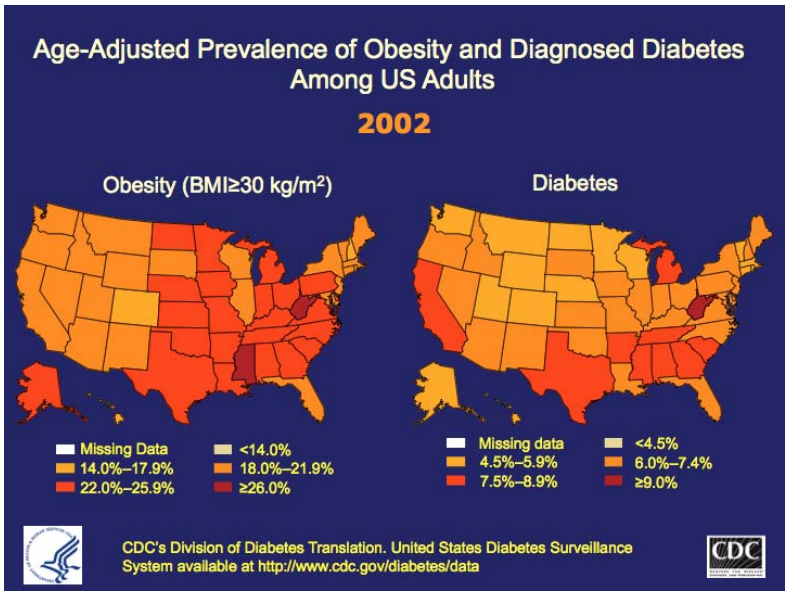
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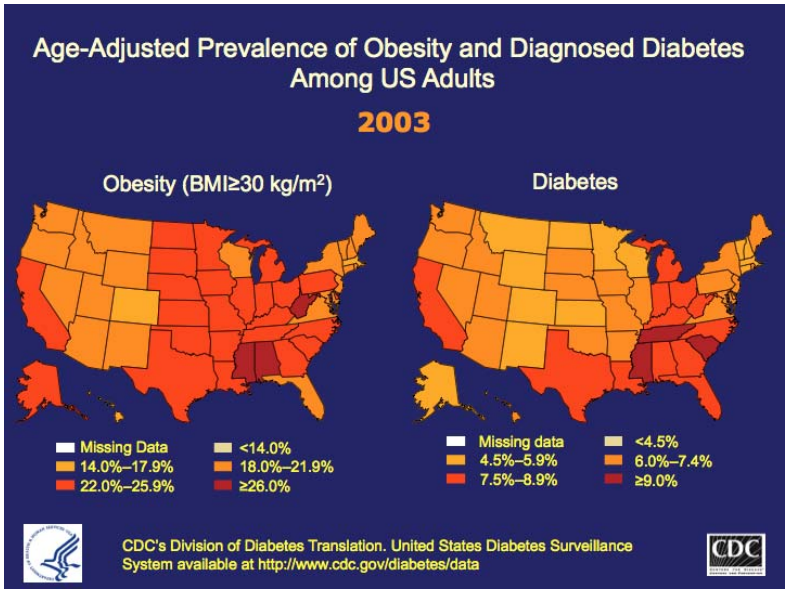
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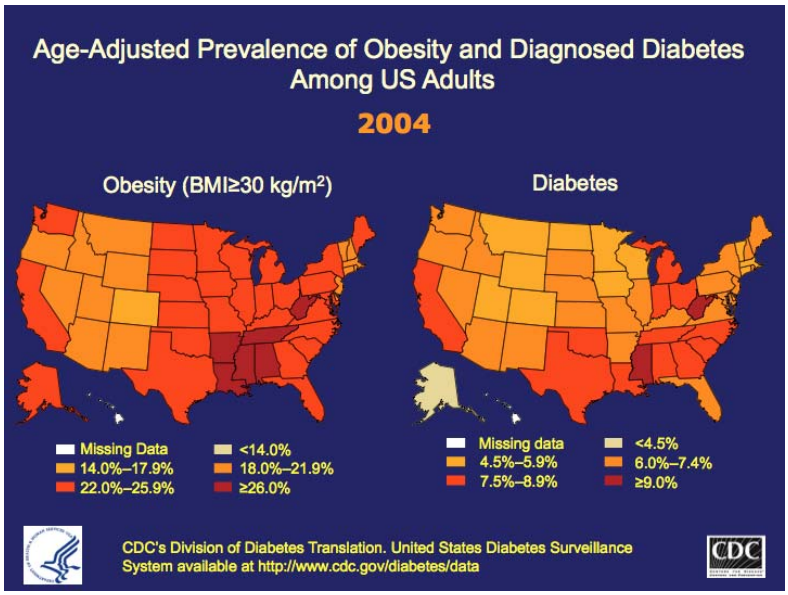
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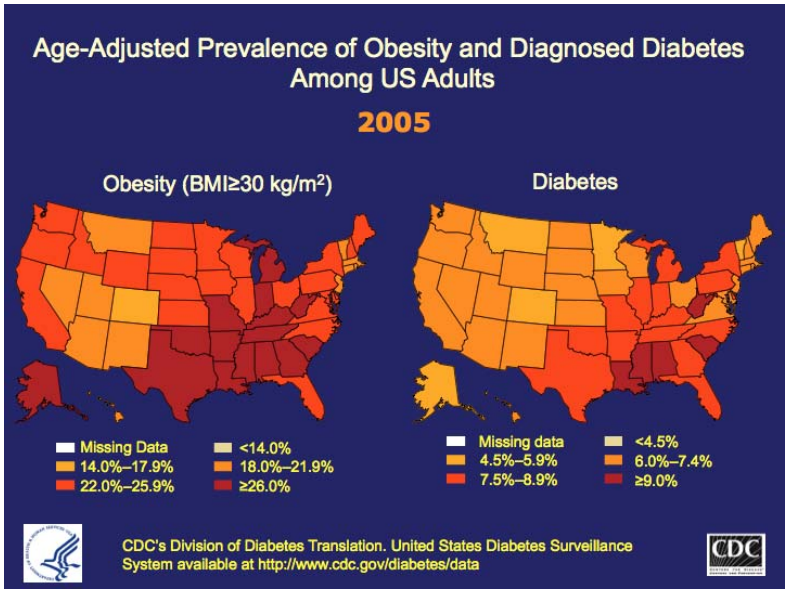
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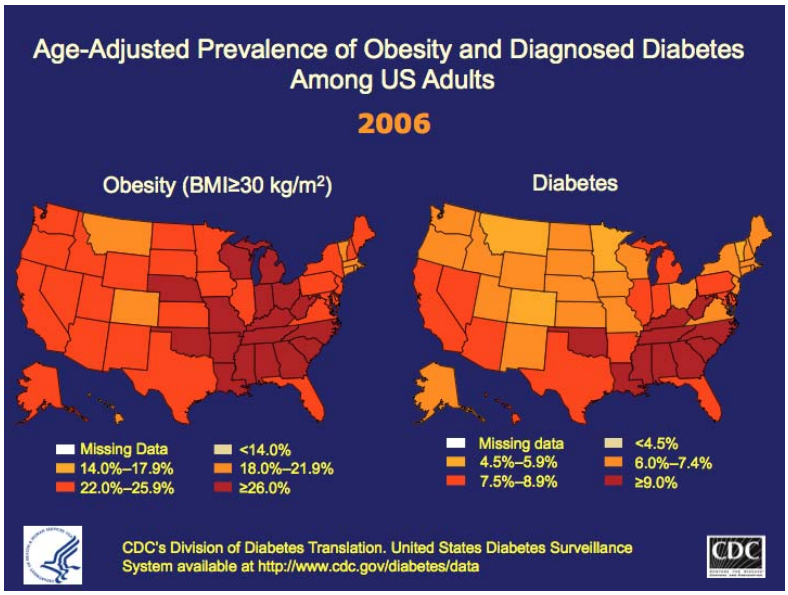
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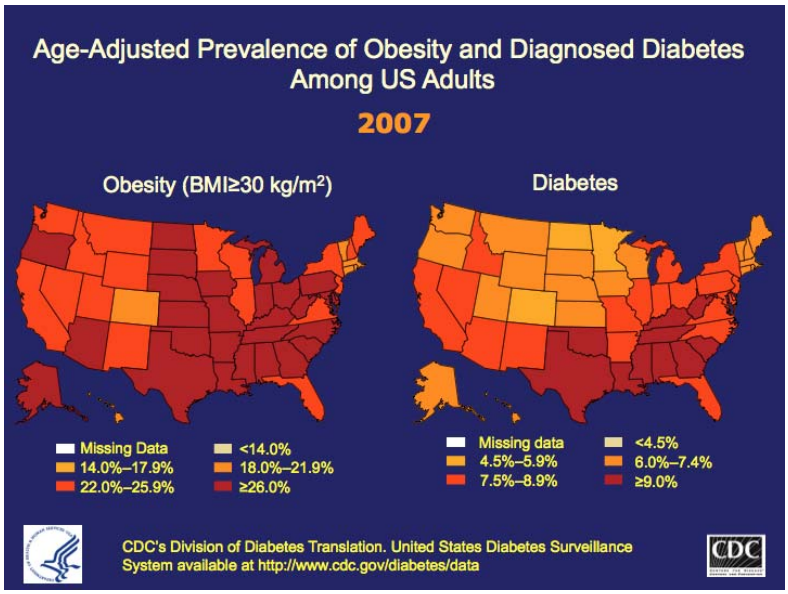
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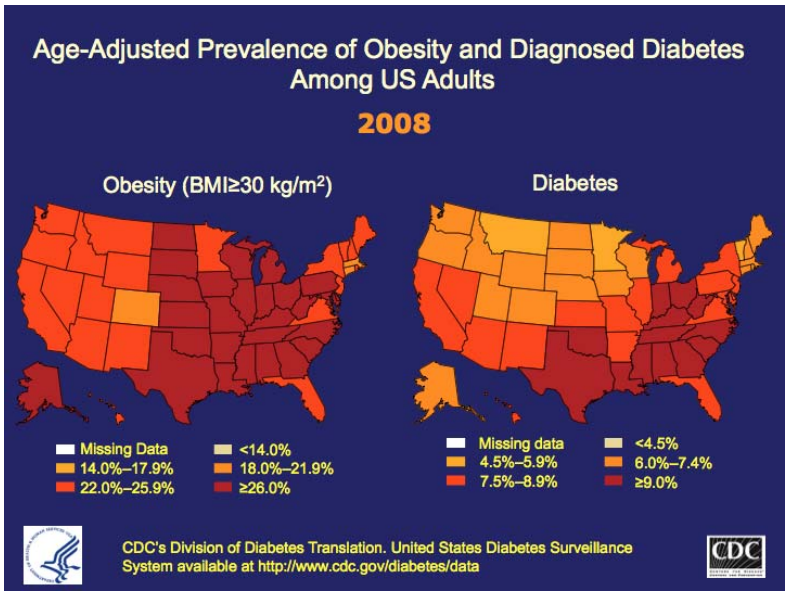
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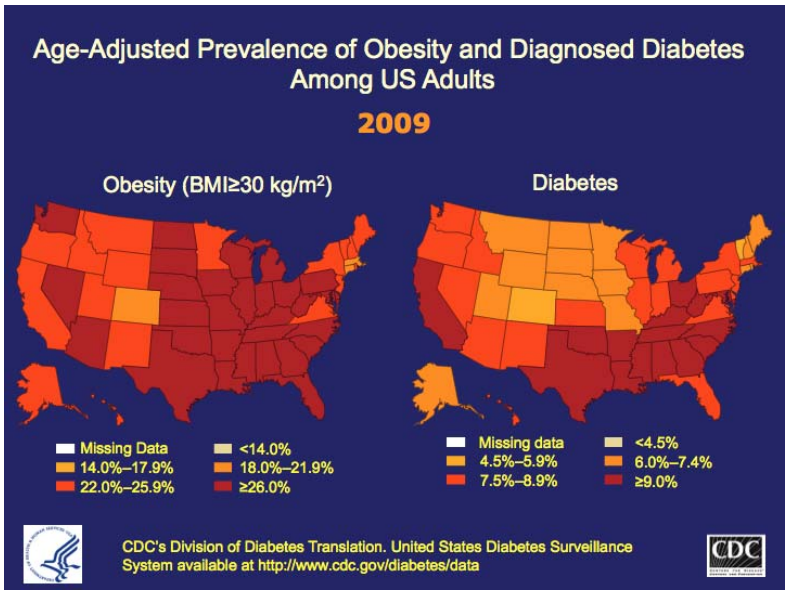
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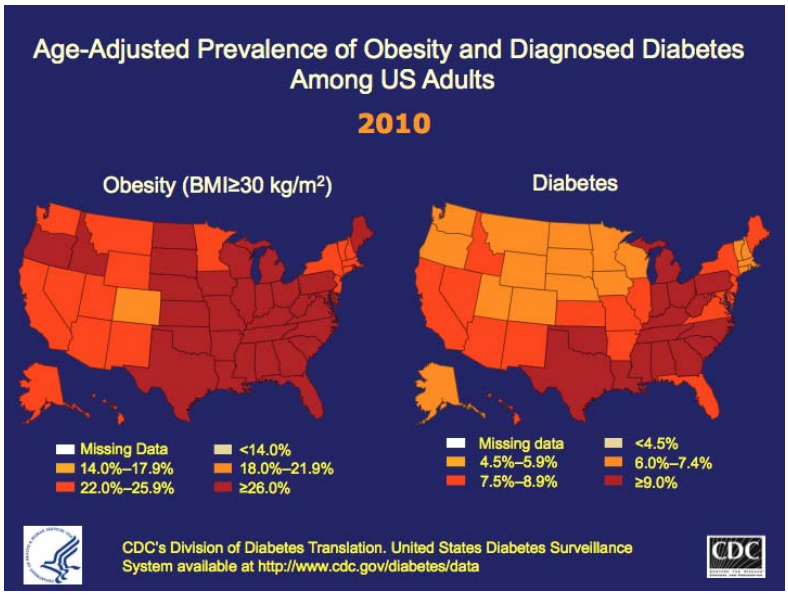
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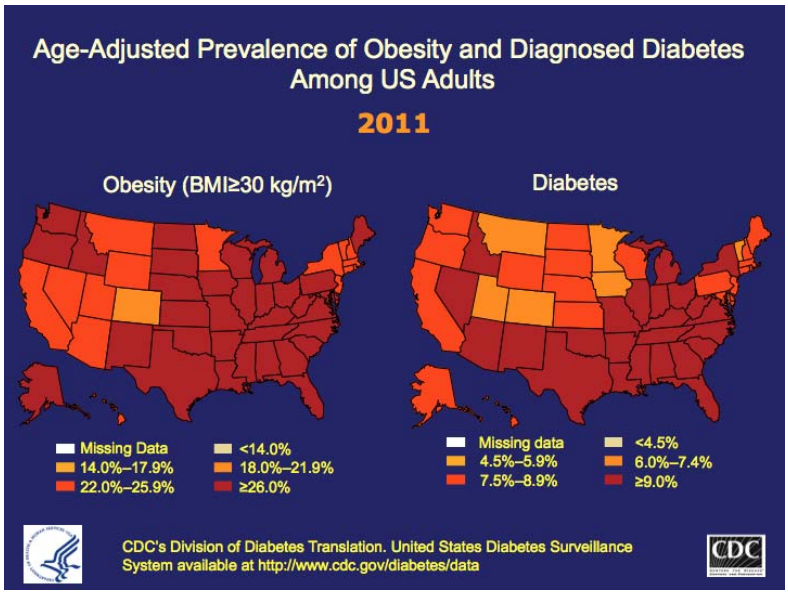
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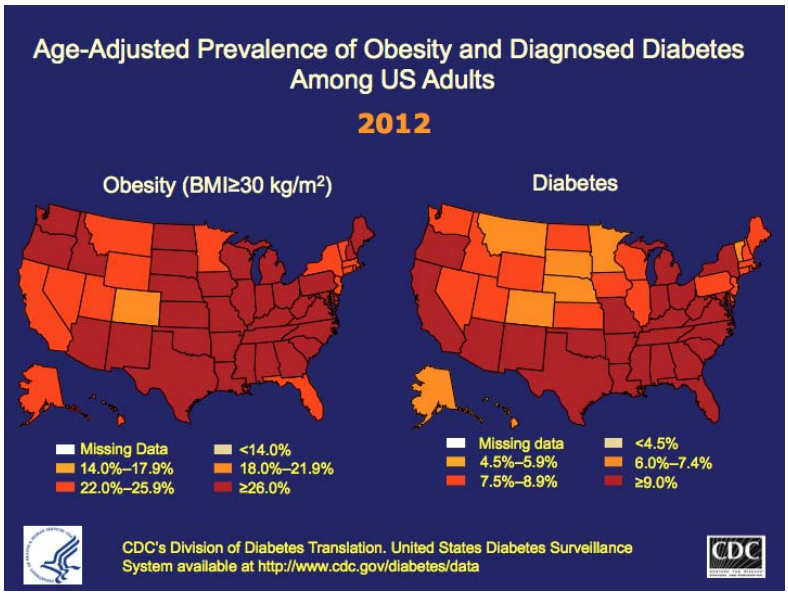
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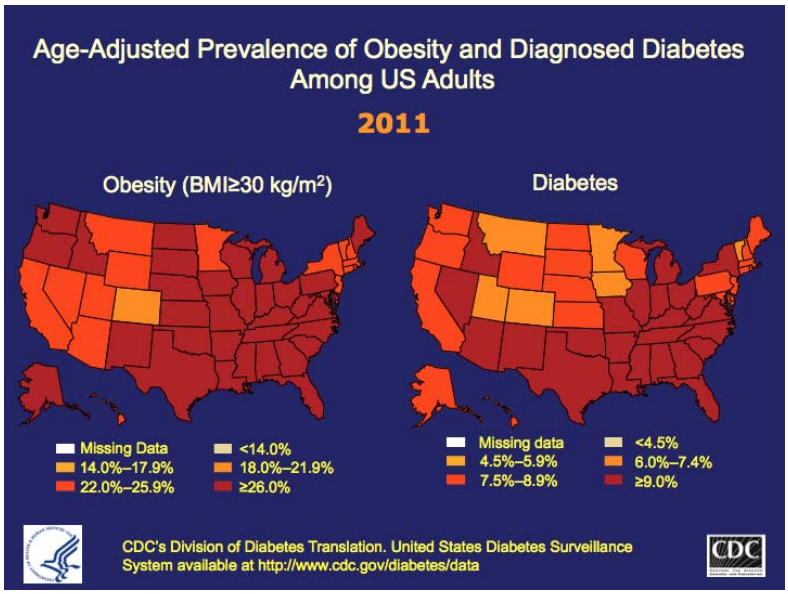
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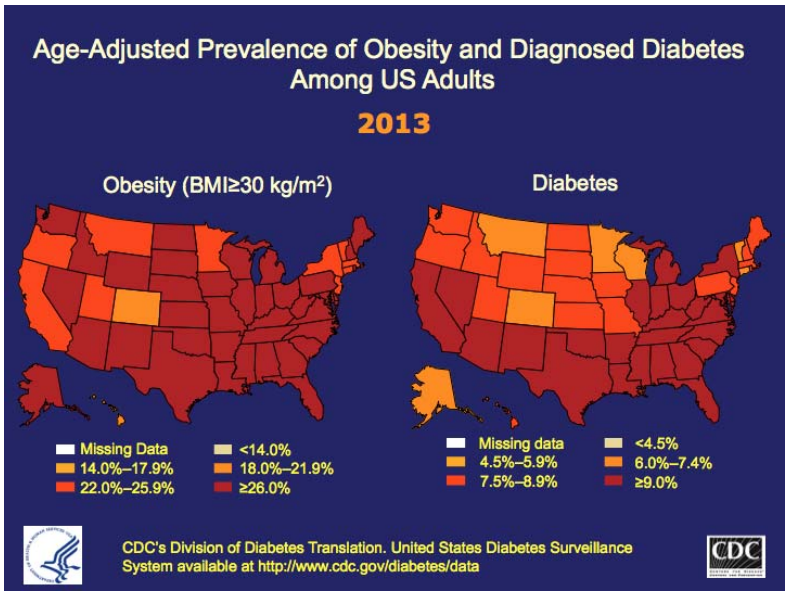
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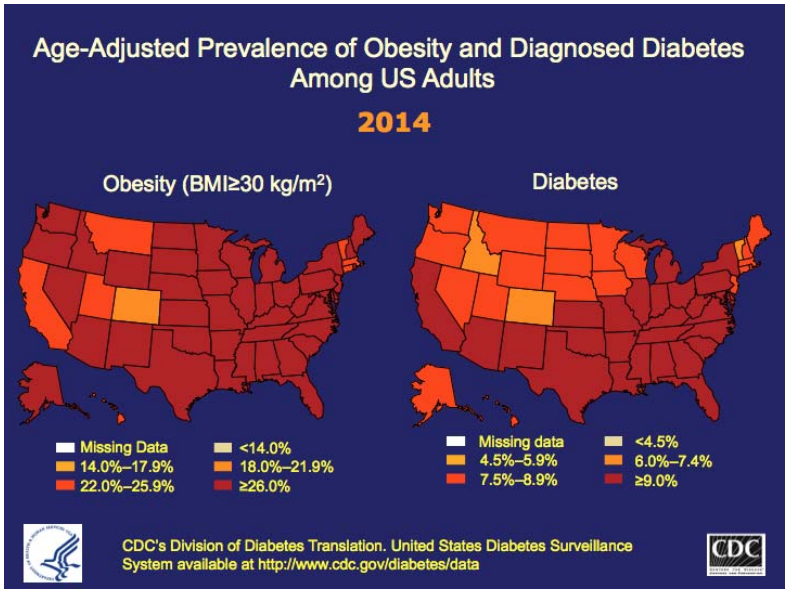
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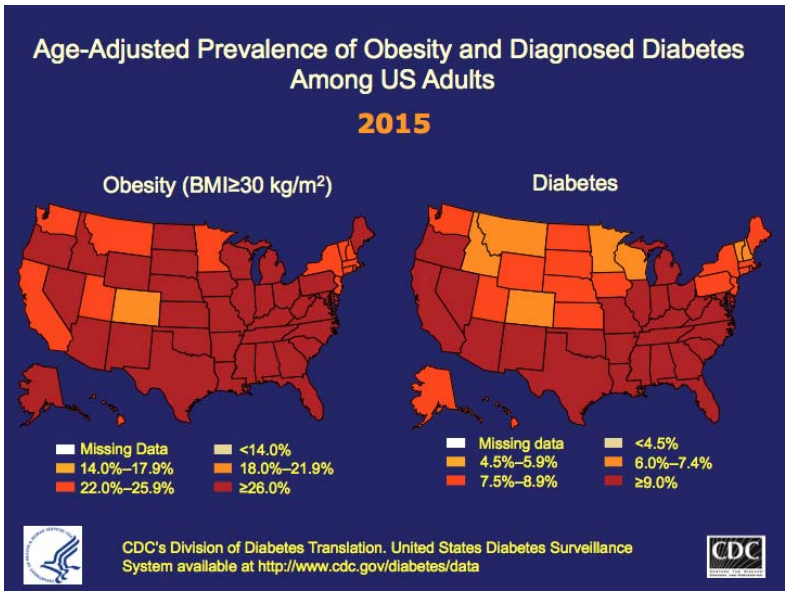
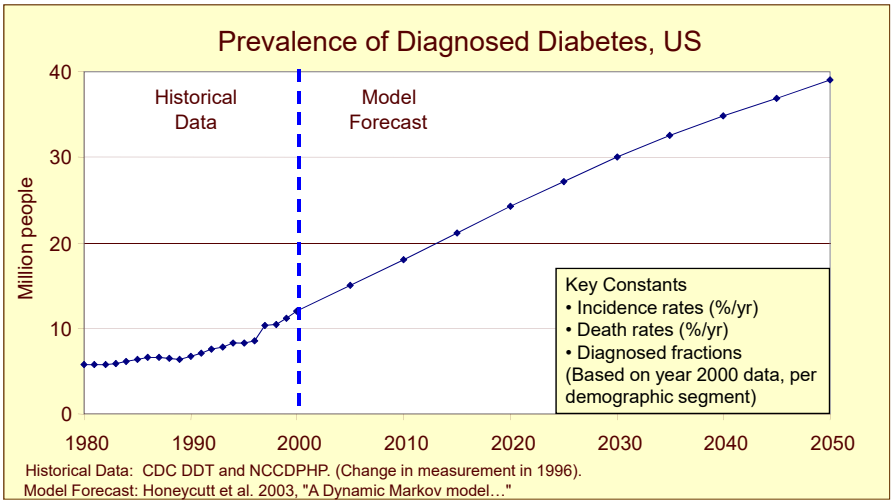


Forecast of Diabetes Prevalence



Honeycutt A, Boyle J, Broglio K, Thompson T, Hoerger T, Geiss L, Narayan K. A dynamic markov model for forecasting diabetes prevalence in the United States through 2050. *Health Care Management Science* 2003;6:155-164.

Hope

"Every new insight into Type 2 diabetes... makes clear that it can be avoided--and that the earlier you intervene the better. The real question is whether we as a society are up to the challenge... Comprehensive prevention programs aren't cheap, but the cost of doing nothing is far greater..."

Gorman C. *Why so many of us are getting diabetes: never have doctors known so much about how to prevent or control this disease, yet the epidemic keeps on raging. how you can protect yourself.* Time 2003 December 8. Accessed at http://www.time.com/time/covers/1101031208/story.html.

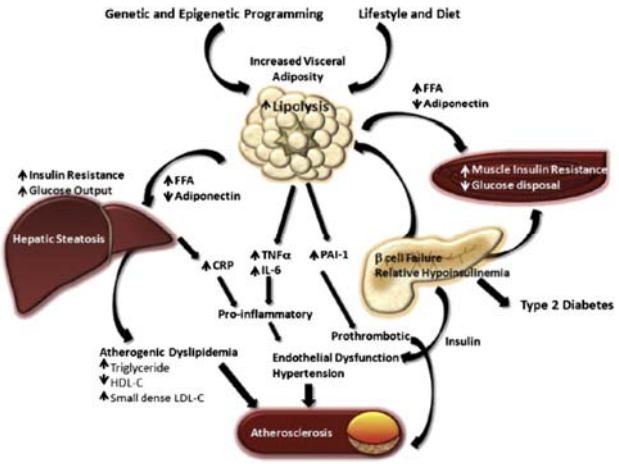
Complications of Obesity

- Metabolic Syndrome
- Non- alcoholic fatty liver disease (NAFLD)
- Dyslipidemia
- Insulin Resistance/ Prediabetes
- Diabetes

Metabolic syndrome

- Developed by National Cholesterol Education Program Adult Treatment Panel III
- 3 of 5 risk factors predict diabetes and CVD
  - Hyperglycemia
  - Increased central adiposity
  - Elevated triglycerides
  - Decreased HDL
  - Elevated blood pressure
- Less defined in pediatrics

Schematic of metabolic syndrome



Dyslipidemia

- Increased insulin --> hepatic lipogenesis--> Release of free fatty acids and triglycerides--> further fat deposition

NAFLD

- Adipose cell hypertrophy --> insulin resistance --> impairs lipolysis suppression--> preference to visceral fat including locations such as liver--> cytokine release--> increased inflammation and ROS

Prediabetes

- Fasting glucose 100-125 mg/dL
- 140-175 mg/dL after glucose tolerance test
- HbA1c 5.7-6.4
- 5-10% progression to diabetes annually

Risk factors

- (1) first- or second-degree relative with T2DM,
- (2) minority race/ethnicity,
- (3) signs of insulin resistance (acanthosis nigricans) or comorbidities (hypertension, dyslipidemia, polycystic ovarian syndrome)
- (4) mother with diabetes or gestational diabetes during child's gestation.

Aditi Khokhar MBBS, Vatcharapan Umpaichitra MD, Vivian L. Chin MD and Sheila Perez-Colon MD
Pediatric Clinics of North America, "Metformin Use in Children and Adolescents." 2017-12-01, Volume 64, Issue 6, Pages 1341-1353,

TABLE 5 Findings on Review of Systems in Obesity Assessment and Possible Causes

Symptom	Possible Causes
Anxiety, school avoidance, social isolation	Depression
Severe recurrent headaches	Pseudotumor cerebri
Shortness of breath, exercise intolerance	Asthma, lack of physical conditioning
Snoring, apnea, daytime sleepiness	Obstructive sleep apnea, obesity hypoventilation syndrome
Sleepiness or wakefulness	Depression
Abdominal pain	Gastroesophageal reflux disease, constipation, gallbladder disease, NAFLD[a]
Hip pain, knee pain, walking pain	Slipped capital femoral epiphysis, musculoskeletal stress from weight (may be barrier to physical activity)
Foot pain	Musculoskeletal stress from weight (may be barrier to physical activity)
Irregular menses (<9 cycles per y)	Polycystic ovary syndrome; may be normal if recent menarche
Primary amenorrhea	Polycystic ovary syndrome, Prader-Willi syndrome
Polyuria, polydipsia	Type 2 diabetes mellitus[a]
Unexpected weight loss	Type 2 diabetes mellitus[a]
Nocturnal enuresis	Obstructive sleep apnea
Tobacco use	Increased cardiovascular risk; may be used as form of weight control

[a] These conditions are often asymptomatic.

TABLE 6 Physical Examination Findings in Obesity Assessment and Possible Causes

System	Findings	Possible Explanations
Anthropometric features	High BMI percentile	Overweight or obesity
	Short stature	Underlying endocrine or genetic condition
Vital signs	Elevated blood pressure	Hypertension if systolic or diastolic blood pressure >95th percentile for age, gender, and height on ≥3 occasions
Skin	Acanthosis nigricans	Common in obese children, especially when skin is dark; increased risk of insulin resistance
	Excessive acne, hirsutism	Polycystic ovary syndrome
	Irritation, inflammation	Consequence of severe obesity
	Violaceous striae	Cushing syndrome
Eyes	Papilledema, cranial nerve VI paralysis	Pseudotumor cerebri
Throat	Tonsillar hypertrophy	Obstructive sleep apnea
Neck	Goiter	Hypothyroidism
Chest	Wheezing	Asthma (may explain or contribute to exercise intolerance)
Abdomen	Tenderness	Gastroesophageal reflux disorder, gallbladder disease, NAFLD[a]
	Hepatomegaly	NAFLD[a]
Reproductive system	Tanner stage	Premature puberty in <7-y-old white girls, <6-y-old black girls, and <9-y-old boys
	Apparent micropenis	May be normal penis that is buried in fat
	Undescended testes	Prader-Willi syndrome
Extremities	Abnormal gait, limited hip range of motion	Slipped capital femoral epiphysis
	Bowing of tibia	Blount disease
	Small hands and feet, polydactyly	Some genetic syndromes

[a] These conditions are usually without signs.

Table 2. Screening for Comorbidities of Pediatric Overweight or Obesity

Comorbidity	Tests and Interpretation	Source
Prediabetes HbA1c	5.7% to <6.5% (39 to <48 mmol/mol) (note the unpredictability of this test in pediatrics in the text)[a]	American Diabetes Association (59)
IFG (verify fasting status)	Fasting plasma glucose of ≥100 but <126 mg/dL (≥5.6 but <7.0 mmol/L)	
IGT (if OGTT is used)	Two-hour glucose of ≥140 but <200 mg/dL (≥7.8 but <11.1 mmol/L)	
Diabetes mellitus	HbA1c ≥ 6.5% (≥48 mmol/mol)[a,b] Fasting plasma glucose of ≥126 mg/dL (≥7.0 mmol/L) (fasting is defined as no caloric intake for 8 h)[b] Two-hour plasma glucose of ≥200 mg/dL (≥11.1 mmol/L) during an OGTT[b] In a patient with classic symptoms of hyperglycemia, a random plasma glucose of ≥200 mg/dL	American Diabetes Association (59)
Dyslipidemia	Fasting lipids Triglycerides (mg/dL) (multiply by 0.0113 to convert to mmol/L): 0–9 y < 75 (acceptable), 75–99 (borderline high), ≥100 (high); 10–19 y < 90 (acceptable), 90–129 (borderline high), ≥130 (high) LDL cholesterol (mg/dL) (multiply by 0.0259 to convert to mmol/L): <110 (acceptable), 110–129 (borderline high), ≥130 (high) Total cholesterol (mg/dL) (multiply by 0.0259 to convert to mmol/L): <170 (acceptable), 170–199 (borderline high), ≥200 (high) HDL cholesterol (mg/dL) (multiply by 0.0259 to convert to mmol/L): <40 (low), 40–45 (borderline low), >45 (acceptable) Non–HDL cholesterol (mg/dL) (multiply by 0.0259 to convert to mmol/L) (can be nonfasting) <120 (acceptable), 120–144 (borderline high), ≥145 (high)	Expert Panel Summary Report (58)
Prehypertension and hypertension	3–11 y: (standardized according to sex, age, and height percentile) BP > 90th percentile to <95th percentile = prehypertension BP ≥ 95th percentile to <99th percentile + 5 mm Hg = stage 1 HTN BP ≥ 99th percentile + 5 mm Hg = stage 2 HTN 12–17 y: (standardized according to sex, age, and height percentile) BP of >90th percentile to <95th percentile or >120/80 = prehypertension BP ≥ 95th percentile to <99th percentile + 5 mm Hg = stage 1 HTN BP ≥ 99th percentile + 5 mm Hg = stage 2 HTN 18 to 21 y: BP ≥ 120/80 to 139/89 mm Hg = prehypertension BP ≥ 140/90 to 159/99 mm Hg = stage 1 HTN BP ≥ 160/100 to 179/109 mm Hg = stage 2 HTN BP > 180/110 mm Hg = stage 3 HTN	Expert Panel Summary Report (58); Mancia *et al.*, 2013 (61)
NAFLD	ALT > 25 U/L (boys) and >22 U/L (girls)	Schwimmer *et al.*, 2010 (62)
PCOS	Free and total testosterone and SHBG, per Endocrine Society PCOS guidelines[c]	Legro *et al.*, 2013 (63)
Obstructive sleep apnea	If positive history, refer to pulmonary for nocturnal polysomnography and if not available overnight oximetry	Wise *et al.*, 2011 (48)
Psychiatric	If positive history, refer to mental health specialist	Zamethkin *et al.*, 2004 (51)

Management

- Dietary & Physical Activity Counseling
- Lab/ Comorbidities screening
- Pharmacotherapy including metformin
- Endocrine/ Surgery referral

Chronic Care Model

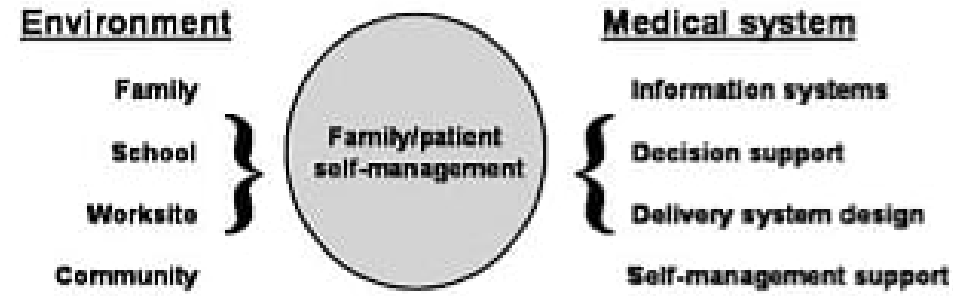
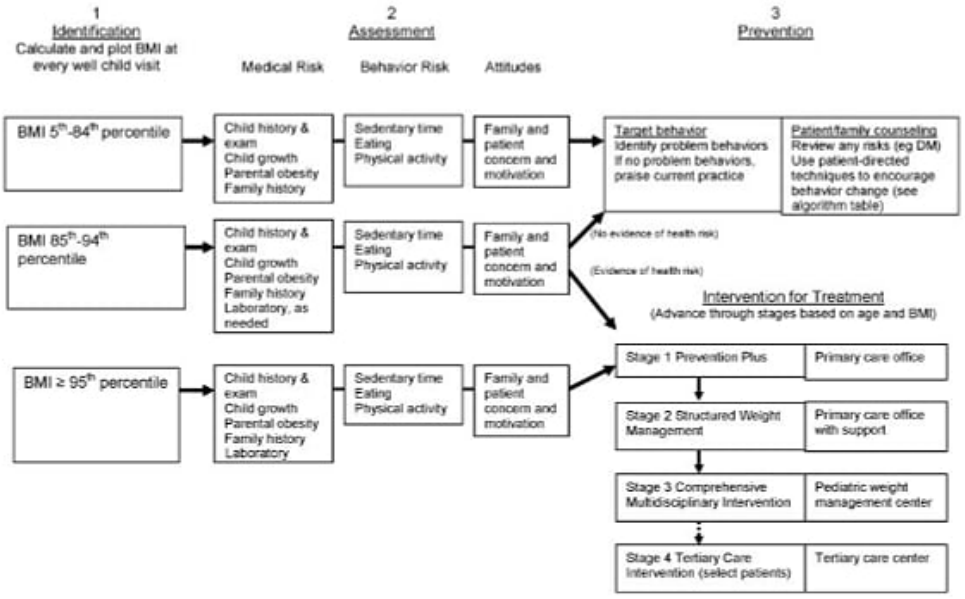


FIGURE 2
Obesity care model.



Counseling

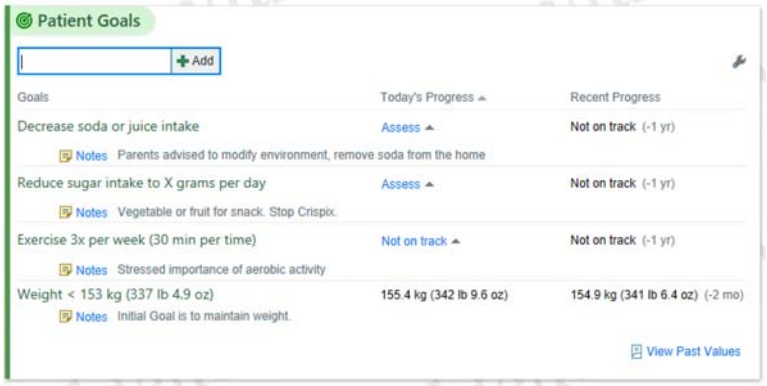
- Healthy food choices
- Exercise
- Sedentary activity
- Sleep hygiene
- Evaluate psychologic comorbidities

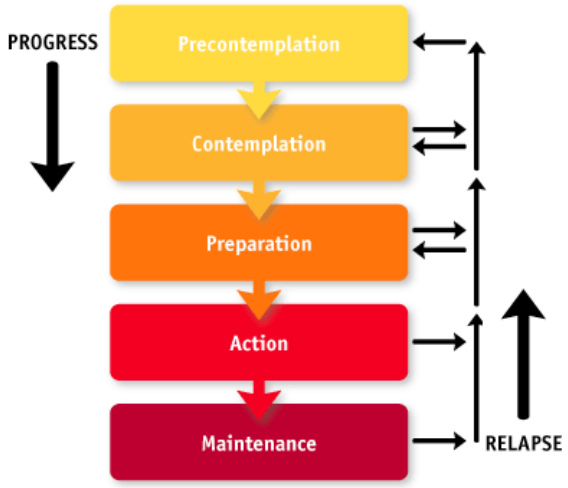
Examples

- portion control education
- reduced saturated dietary fat intake for children and adolescents >2 years of age
- US Department of Agriculture recommended intake of dietary fiber, fruits, and vegetables
- timely, regular meals, and avoiding constant "grazing" during the day, especially after school and after supper
- recognizing eating cues in the child's or adolescent's environment, such as boredom, stress, loneliness, or screen time
- encouraging single portion packaging and improved food labeling for easier use by consumers. (Ungraded Good Practice Statement)
- decreased consumption of fast foods
- decreased consumption of added table sugar and elimination of sugar-sweetened beverages
- decreased consumption of high-fructose corn syrup and improved labeling of foods containing high-fructose corn syrup
- decreased consumption of high-fat, high-sodium, or processed foods
- consumption of whole fruit rather than fruit juices

Approach

- Targeted
- Written
- Achievable
- Family- Engaged
- Patient- Centered
- Success- focused





Does metformin prevent/ delay onset of type II diabetes in children with obesity or insulin resistance?

Metformin

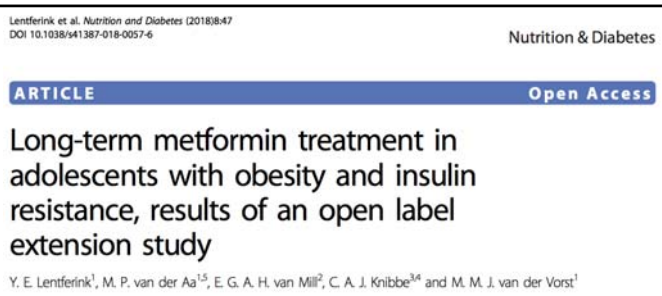
- For obese, non-diabetic patients, improvement in
  - Fasting glucose
  - Insulin level
  - BMI
  - Cholesterol
  - Blood pressure
- Small studies with conflicting magnitude of effect
- Meta- analysis (McDonagh) confirms small, short- term benefit for BMI

Summary of Studies for Metformin in Prediabetes

Study	Inclusion Criteria	n; Age (y)	Design/Duration	Therapy	Major Findings
Freemark and Bursey, [37] 2001 (United States)	BMI >30 kg/m ^{2} ; fasting insulin >15 μU/mL and family history of T2DM	29; 12–19	RCT/6 mo	Metformin 500 mg twice daily vs placebo No lifestyle modifications	Significant improvement in BMI, fasting insulin and FPG No significant change in insulin sensitivity, HbA1c or lipid profile
Kay et al, [32] 2001 (United States)	BMI >30 kg/m ^{2} ; Fasting glucose <120 mg/dL, HbA1c <7%, normal OGTT	24; 15.6 ± 0.4 (metformin group), 15.7 ± 0.5 (placebo group)	RCT/8 wk	Metformin 850 mg twice daily vs placebo; low calorie diet	Reduction in body weight, body fat, fasting insulin, AUC insulin and leptin concentrations. No significant change in FPG
Srinivasan et al, [45] 2006 (Australia)	Obesity as defined by the International Obesity Task Force; fasting insulin (mu/L) to fasting glucose (mmol/L) ratio >4.5 or presence of acanthosis nigricans	28; 9–18	RCT with crossover at 6 months/12 mo	Metformin 1000 mg twice daily vs placebo No lifestyle intervention	Significant improvements in weight, BMI, and waist circumference, abdominal subcutaneous fat, fasting insulin and FPG No significant change in visceral fat or insulin sensitivity
Fu et al, [51] 2007 (China)	Weight >97th percentile, and >30% or 50% of weight for age and gender	30; 7–16	Observational uncontrolled study/3 mo	Metformin 500 mg twice daily with lifestyle modifications	Significant reductions in BMI, adiponectin level, HOMA-IR, cholesterol, triglyceride and 2-h plasma glucose
Atabek and Pirgon, [42] 2008 (Turkey)	BMI >95th percentile	120; 9–17	RCT/6 mo	Metformin 500 mg twice daily with individualized diet and exercise regimen	Significant reduction in BMI, fasting insulin levels, improvement in HOMA-IR and QUICKI and insulin AUC
Love-Osborne et al, [44] 2008 (United States)	Fasting insulin >25 μU/mL or HOMA-IR >3.5 and 2 out of 3 factors (acanthosis nigricans, BMI >95th percentile, family history of T2DM)	85; 12–19	RCT/6 mo	Metformin 850 mg twice daily, goal setting for lifestyle modifications	No overall difference in weight loss between metformin and placebo group No differences in insulin level changes in the 2 groups
Clarson et al, [43] 2009 (Canada)	BMI >95th percentile, HOMA-IR >3.0	25, 10–16	RCT/6 mo	Metformin 1500 mg daily with lifestyle interventions	Significant reductions in BMI but no change in HOMA
Wiegand et al, [41] 2010 (Germany)	No success after 6 mo of lifestyle interventions in patients with BMI >97th percentile: ΔBMP <2, HOMA-IR >3 or 95th percentile	70, 12–18	RCT/6 mo	Metformin 500 mg twice daily with continued lifestyle intervention	No significant change in BMI or HOMA-IR, improved insulin sensitivity
Wilson et al, [48] 2010 (United States)	BMI >95th percentile	77; 13–18	RCT/12 mo	Metformin 2000 mg extended release once daily with lifestyle interventions	Small but significant improvement in BMI that persisted at 12–24 wk after cessation of medication No significant changes in central adiposity, insulin indices, or lipid indices

Aditi Khokhar MBBS, Vatcharapan Umpaichitra MD, Vivian L. Chin MD and Sheila Perez-Colon MD
Pediatric Clinics of North America, "Metformin Use in Children and Adolescents." 2017-12-01, Volume 64, Issue 6, Pages 1341-1353,

Yanovski et al, [46] 2011 (United States)	BMI ≥95th percentile	100; 6–12 y	RCT for 6 mo followed by 6 mo open-label metformin	Metformin 1000 mg twice daily along with lifestyle interventions	Significant reduction in weight, BMI, body fat, body circumference and skin fold thickness Improved fasting insulin, FPG and HOMA-IR No change in first phase insulin secretion of insulin sensitivity
Gómez-Díaz et al, [52] 2012 (Mexico)	Impaired glucose tolerance on OGTT per ADA criteria	52; 4–17	RCT/3 mo	Metformin 850 mg twice daily vs placebo; with consistent individualized diet and exercise regimen	Significant reductions in percentage weight change, resistin concentrations, HOMA-IR, HbA1c, AST, and ALT After adjusting for weight loss, only HbA1c and resistin reductions were significant
Rynders et al, [53] 2012 (United States)	BMI >95th percentile	16; 10–17	Not placebo controlled/6 mo	Metformin 500 mg twice daily (<12 y), 1000 mg twice daily (≥12 y) with lifestyle intervention	No benefit on body composition or inflammatory markers
Mauras et al, [40] 2012 (United States)	BMI >95th percentile, CRP and/or fibrinogen >2 SD above mean	42; 8–17	Not placebo controlled/6 mo	Metformin 500 mg twice daily (<12 y), 1000 mg twice daily (≥12 y) with lifestyle intervention	Improved BMI and waist circumference Inflammatory markers were improved in the lifestyle intervention only group compared with metformin and lifestyle intervention group
The MOCA Trial, 2013 (UK) [28]	BMI >98th percentile; and OGTT 2-h plasma glucose ≥7.8 to ≤11.1 mmol/L (with or without impaired fasting glucose ≥6.1 to ≤7.0 mmol/L), or fasting insulin >26 mIU/L or 120-min insulin >89 mIU/L (pubertal/postpubertal children); fasting insulin >15 mIU/L or 120-min insulin >89 mIU/L (prepubertal children)	151; 8–18	Multicenter RCT/6 mo	Metformin 1000 mg in morning and 500 mg in evening vs placebo Not intensive lifestyle intervention	Significant improvements in BMI at 3 and 6 mo Improvements in FPG, AST, and adiponectin/leptin ratio at 3 mo No changes in adiponectin, resistin, or leptin concentrations No effect on CRP, fasting lipid, and fasting insulin levels
Van der Aa et al, [53] 2016 (Netherlands)	BMI SDS >2.3, HOMA-IR ≥3.4	42; 10–16	Multicenter RCT/18 mo	Metformin 1000 mg twice daily with lifestyle interventions	BMI improved at 6–9 mo interval but was back to baseline at 18 mo No improvement in HOMA-IR or A1c Improvement in fat mass, no change in body fat percentage



Lentferink et al. *Nutrition and Diabetes* (2018)8:47
DOI 10.1038/s41387-018-0057-6

Nutrition & Diabetes

ARTICLE Open Access

Long-term metformin treatment in adolescents with obesity and insulin resistance, results of an open label extension study

Y. E. Lentferink[1], M. P. van der Aa[1,5], E. G. A. H. van Mill[2], C. A. J. Knibbe[3,4] and M. M. J. van der Vorst[1]

- 42 participants
- Case-Control Design
- Outcome: BMI-z and Insulin Resistance
- Conclusion: Metformin provided short-term improvements but findings weren't sustained at 18 months

Metformin in Obese Children and Adolescents: The MOCA Trial FREE

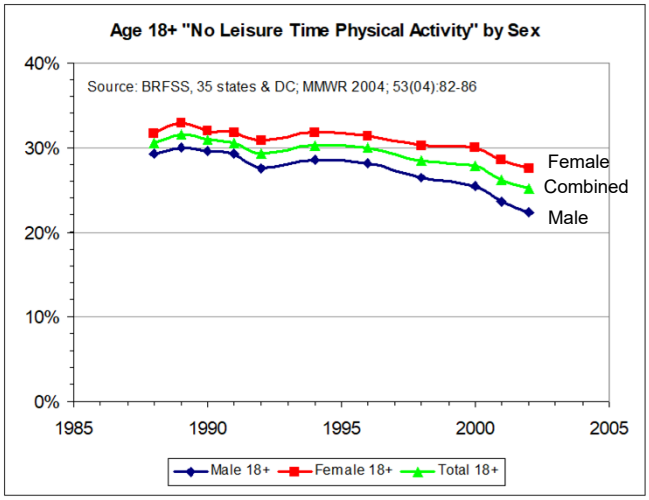
D. Kendall ✉, A. Vail, R. Amin, T. Barrett, P. Dimitri, F. Ivison, M. Kibirige, V. Mathew, K. Matyka, A. McGovern, ... Show more

The Journal of Clinical Endocrinology & Metabolism, Volume 98, Issue 1, 1 January 2013, Pages 322–329, https://doi.org/10.1210/jc.2012-2710

- 151 obese children in RCT
- Randomized to metformin & placebo
- BMI change for 3 & 6 months
- BUT fasting glucose, ALT, and adiponectin/ leptin for 3 months but not 6 months

Marginal Gains in Physically Active Individuals

Adult "No Leisure Time Physical Activity" (BRFSS)



Metformin side effects

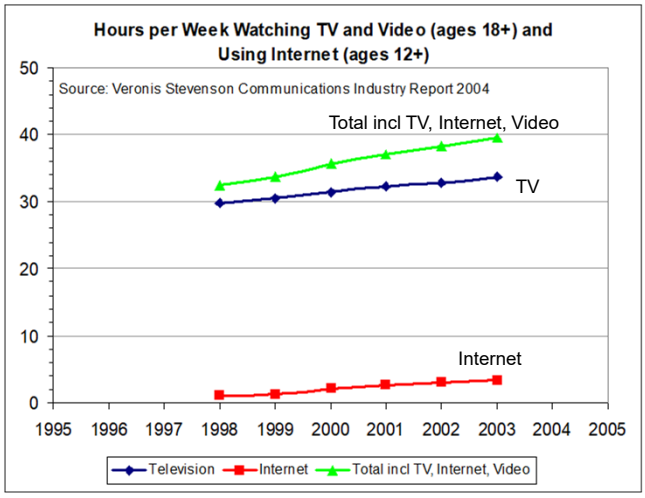
- Abdominal pain
- Nausea
- Bloating
- Diarrhea
- Metallic taste
- Lactic acidosis

Metformin

- Endocrine Society recommends against metformin in management of obesity BUT
- Consider in patient with
  - Obesity
  - Co-mordities
  - Engagement
- Evaluate response

Increasing Sedentary Activity

Hours per Week Watching TV, Internet, Video (Media Industry Report)



From "Understanding Obesity Dynamics", *A Foundation for Directing Change and Charting Progress.* CDC. 2005

Some Sources of Complexity for Obesity

Multiple Goals

- Improve diet
- Increase physical activity
- Decrease physical inactivity
- Assure healthful conditions in diverse behavioral settings (i.e., home, school, work, community)
- Harness synergies with other social values (i.e., school performance, economic productivity, environmental protection)

Simultaneous Program Strategies

- Deliver healthcare services
- Enhance media messages
- Expand options in behavioral settings
- Modify trends in the wider environment (i.e., economy, technology, laws)
- Address other health conditions that impede healthy diet and activity (e.g., asthma, oral health, etc.)

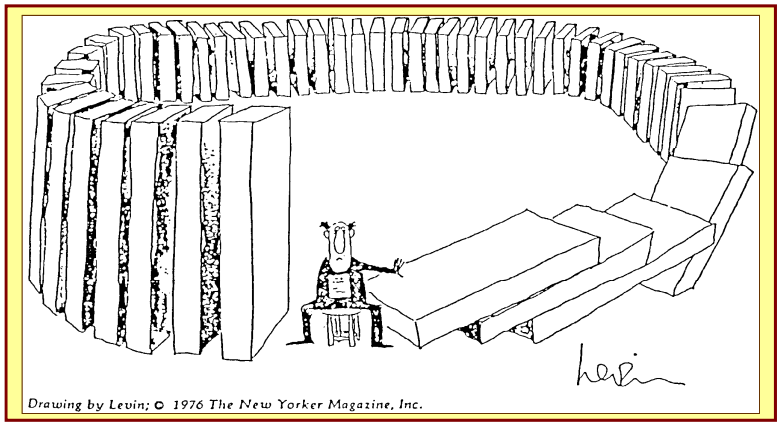
Barriers

- Cost of caring for weight-related diseases
- Cost of health protection efforts
- Spiral of unhealthy habits leading to poor health leading to even less healthy habits
- Social reinforcement of diet and activity based on observing parents', peers', and others' behavior
- Demand for unhealthy food and inactive habits stimulates supply
- Resistance by defenders of the status quo

Time Delays

- 1-2 year lag for metabolism to stabilize after change in net caloric intake
- 14 year lag for youth to age into adulthood
- 58 year lag for cohorts of adults
- Several years for programs to mature and for policies to be fully enacted/enforced
- At least several years to see policy impacts, and even longer to affect the wider environment

Complexity is Real… and Consequential



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Referral

Endocrinology

- Criteria for diabetes
- Hypothyroidism

Bariatric Surgery

- Tanner IV or V, BMI >40 or 35 w/ comorbidities
- Refractory to compliance with stage III intervention
- Absence of psychologic impairment
- Adherence to dietary regimen
- Access to bariatric team

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