Keystone Symposium

March 27, 2007

Obesity, Risk Factors and CV Disease: NHLBI Perspectives

Elizabeth G. Nabel, M.D.
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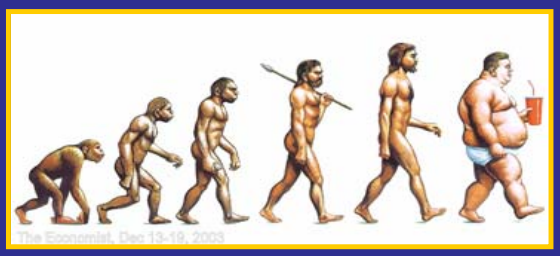
National Heart, Lung, and Blood Institute

Obesity and its risk for Cardiovascular Disease

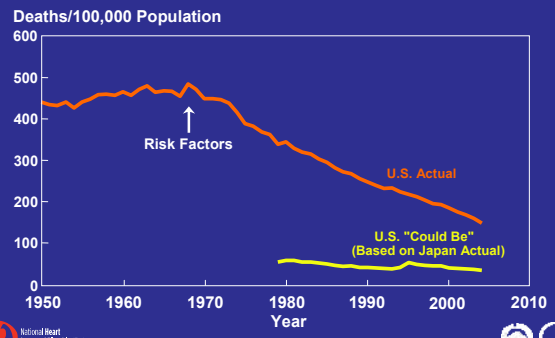


The Economist, Dec 13-19, 2003

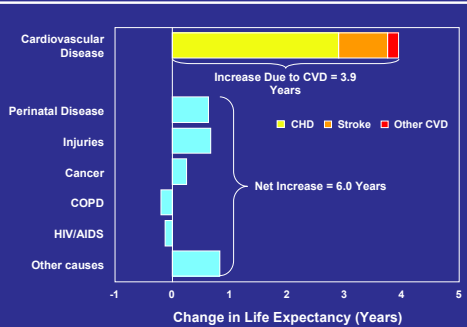
Obesity and CV Disease

- What is the magnitude of obesity in the US?
- Will current trends in obesity reverse the favorable trends in CVD?
- What is known about the relationship between obesity, its associated risk factors and CVD?
- Which interventions are effective?

Age-Adjusted Death Rates for Coronary Heart Disease, U.S., 1950-2004

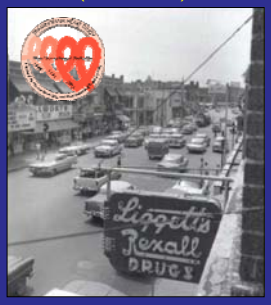


Contributions to Change in Life Expectancy, U.S., 1970-2000



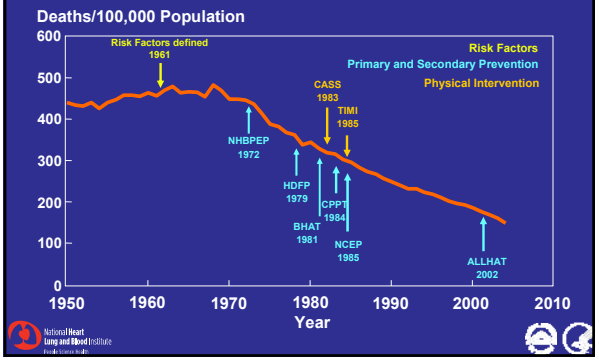
Framingham Heart Study

Downtown Framingham, MA
(circa 1960)



- Risk Factors for Heart Attack and Stroke
  - High blood pressure
  - High cholesterol
  - Cigarette smoking
  - Diabetes mellitus
  - Parental or sibling history
  - Obesity

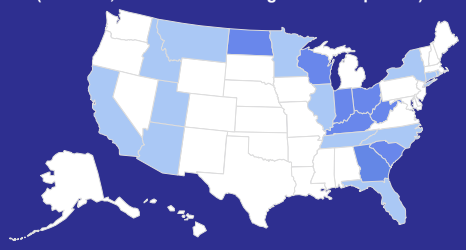
Age-Adjusted Death Rates for Coronary Heart Disease, U.S., 1950-2004



What is the magnitude of obesity in the US?

Obesity Trends* Among U.S. Adults BRFSS, 1985

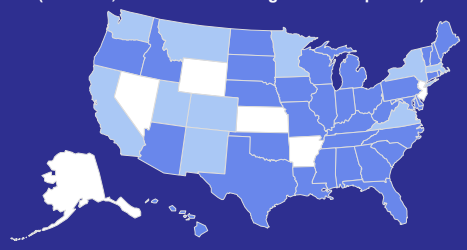
(*BMI ≥30, or ~ 30 lbs overweight for 5' 4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults BRFSS, 1990

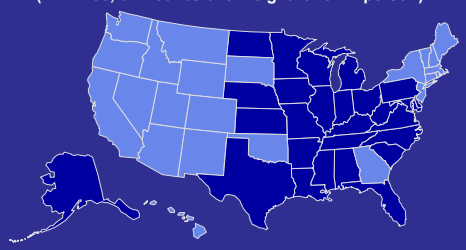
(*BMI ≥30, or ~ 30 lbs overweight for 5' 4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults BRFSS, 1995

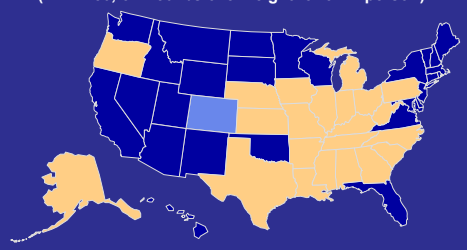
(*BMI ≥30, or ~ 30 lbs overweight for 5' 4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults BRFSS, 2000

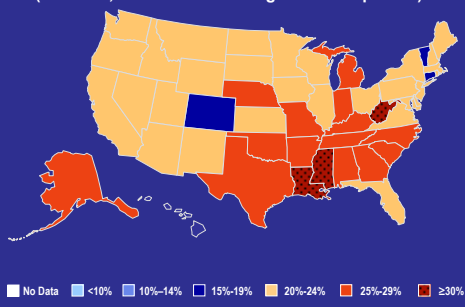
(*BMI ≥30, or ~ 30 lbs overweight for 5' 4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs overweight for 5' 4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

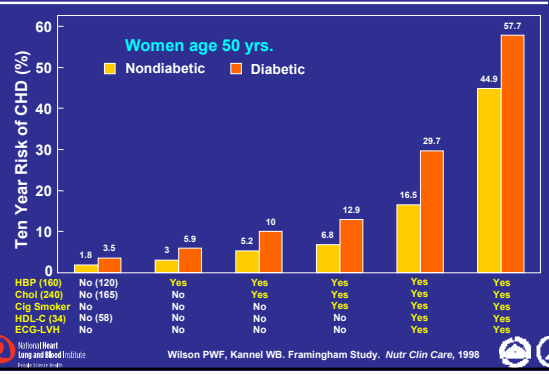
Will current trends in obesity reverse the favorable trends in CVD?

Obesity – Natural Evolution or a Tragic Outcome of the 21st Century

- Complex etiology - old genes in a new environment
- Evolution selected defenses to cope with periods of starvation
- Sustained supply of cheap, high calorie food for masses is unique to the 20th century
- Consequences are predictable – weight gain and subsequent chronic diseases
- May slow the improvement in reducing CVD prevalence and incidence
- Is adding significant costs to our health care system, which will only increase
- Prevention and treatment are possible but will require coordinated efforts

What is known about the relationship between obesity, its associated risk factors and CVD?

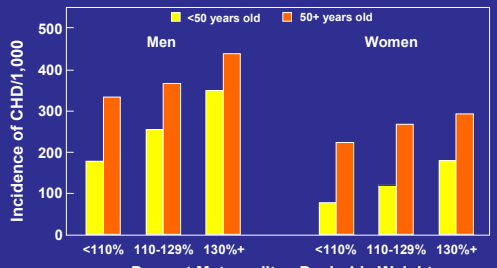
Risk of Coronary Heart Disease by Diabetic Status According to Level of Risk Factors



Wilson PWF, Kannel WB. Framingham Study. *Nutr Clin Care*, 1998

Obesity is an Independent Risk Factor for CHD

Framingham Heart Study (n=5,209, 26-year FU)



Adjusted for age, SBP, cholesterol, smoking, glucose intolerance, LVH

Hubert et al., *Circulation*, 1983

Diabetes and Heart Disease

- Fox et al., Increasing CV D burden due to DM in the FHS, *Circulation* 2007; online March 12
- The proportion of CVD due to DM has increased about 60% over time in the FHS.
- Investigation of 9540 people, ages 45-64, 1952-74 and 1975-98. The percent of heart disease attributable to DM increased from 5.2% to 7.8%

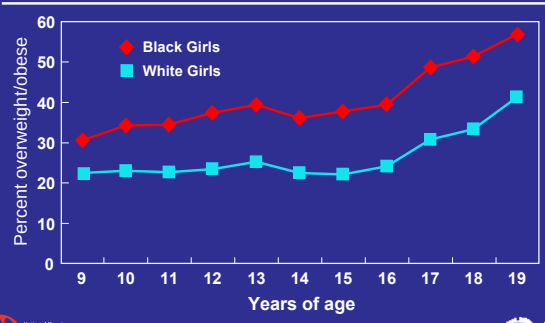
NHLBI Growth and Health Study (NGHS) (1987-1998)

- To examine racial differences in factors related to obesity development
- Cohort of 2379 girls, age 9 or 10 at entry
- 50% white and 50% black, self-identified
- 10 annual visits
- Examined diet, physical activity, psychosocial factors, socioeconomic, and family influences

NGHS Key Findings

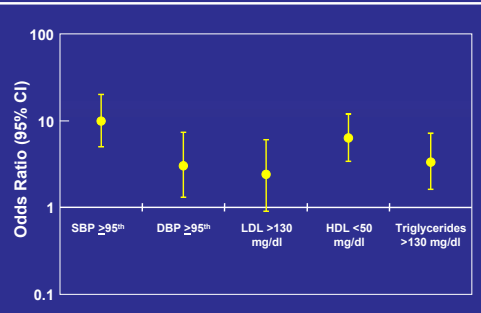
- Black girls had a greater prevalence of obesity than white girls at every age
- Leisure time physical activity declined dramatically throughout adolescence in girls of both races
- Leisure time physical activity was inversely related to BMI and sum of skinfolds
- Caloric intake was not found to be directly related to BMI or adiposity, but frequency of fast food consumption was related to higher caloric intakes in girls of both races

Prevalence of Overweight/Obesity Rises by Age; is Higher in Black than White Girls at All Ages (NGHS)



Kimm et al., *Pediatrics* 2002

NGHS: Odds of CVD Risk Factors in Girls at Age 18 by Overweight Status at Age 9

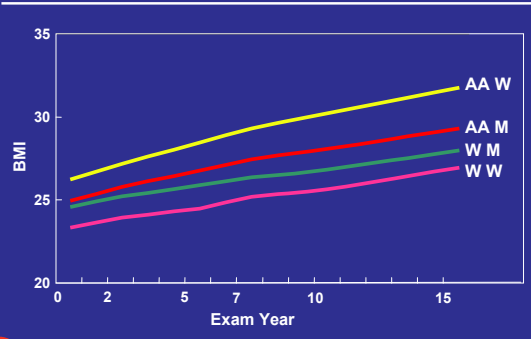


Thompson DR et al., *J Pediatr* 2007; 18-25

Coronary Artery Risk Development in Young Adults (CARDIA) Study

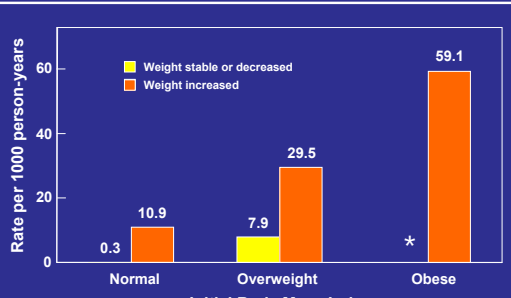
- Multi-center longitudinal study of the development and determinants of CVD risk factors in 18-30 year old African-American and Caucasian young adults first examined in 1985-86
- n= 5,115 at baseline exam
- Balanced by race, sex, education, and age within centers
- Repeat exams at years 2, 5, 7, 10, 15, 20
- 3,549 (72%) returned for year 20 exam

CARDIA: Mean BMI by Exam by Race and Gender, Age 18-30 Years at Baseline



Lewis et al., *Circulation* 2001;104:II-787

CARDIA: 20-Year Incidence of Metabolic Syndrome by Initial and Change in BMI in Adults 18-30

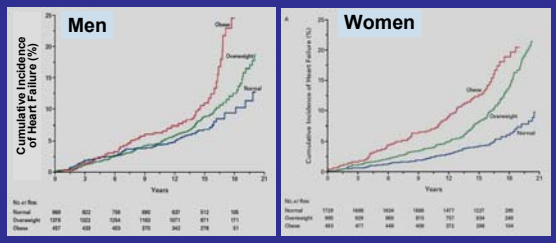


* Too few people to estimate incidence

CARDIA, unpublished data

Overweight and Obesity are Associated with an Increase Incidence of Heart Failure

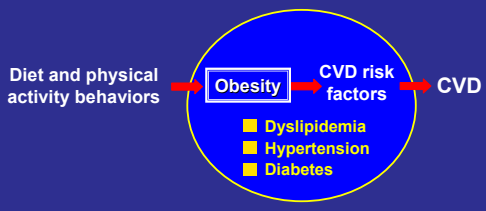
Framingham Heart Study, n=5,881, without heart failure at baseline



HF risk increased 5% for men and 7 % for women per 1 BMI unit
(adjusted for age, alcohol, TC, smoking, valve Dz, HTN, DM, LVH, & MI Hx)

Kenchaiah et al., *N Engl J Med*, 2002

Obesity Affects Other CVD Risk Factors

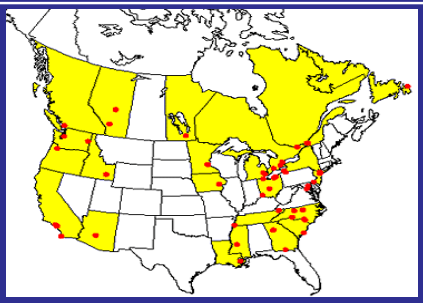


Which interventions are effective?

Action to Control Cardiovascular Disease in Diabetes (ACCORD) Clinical Trial

- Designed to test three separate research questions to reduce CVD in diabetic patients:
  - Glycemia
  - Blood pressure
  - Blood lipids/lipoproteins
- Multi-center randomized clinical trial
- 10,251 patients with type 2 diabetes at high risk for CVD events

ACCORD: Conducted within 7 Clinical Networks at 77 Clinical Sites in US and Canada



Coordinating Center: Wake Forest University
Project Office: NHLBI

ACCORD: Rationale

- Glycemia
  - Glycemia level is directly associated with CVD rates in observational studies
  - Experimental evidence suggest that reducing glycemia will lower CVD
- Hypertension and dyslipidemia
  - Are more common in diabetic persons
  - Optimal treatments for these CVD risk factors in diabetic patients are unknown

ACCORD: Rationale
UKPDS Trial: Major Outcomes (1998)

Outcome	Risk (/1000 p-yrs)		RR (95% CI)	P
	Intensive HbA1c = 7.0% (n=2729)	Conventional HbA1c = 7.9% (n=1138)		
Diabetes Related Endpoint	40.9	46.0	0.88 (0.79-0.99)	0.029
Myocardial Infarction	14.7	17.4	0.84 (0.71-1.00)	0.052
Microvascular Endpoint	8.6	11.4	0.75 (0.60-0.93)	0.0099

ACCORD: Rationale
Clinical Trials of SBP Lowering in Diabetes

Trial	N	Mean SBP, less intense	Mean SBP, more intense	CVD Risk Reduction
SHEP	583	155*	146*	22-56%
Syst-Eur	492	162	153	62-69%
HOT	1,501	144**	140**	30-67%
UKPDS	1,148	154	144	32-44%
ABCD	470	138	132	No CVD reduction

* Personal communication, Sara Pressel: mean BP at 3 yrs of F/U
** BP in diabetic + non-diabetic population

ACCORD: What are the appropriate medical targets to reduce CVD?
Three Medical Strategies

- **Glycemia**
  - Intensive control (HbA1c<6.0%) vs
  - Standard control (HbA1c 7.0%-7.9%)
- **BP**
  - Intensive control (SBP <120 mmHg) vs
  - Standard control (SBP <140 mmHg)
- **Lipids**
  - Fibrates to increase HDL-C and lower TG + statins to lower LDL-C vs
  - Statins to lower LDL-C alone

ACCORD: Double 2 x 2 Factorial Design

	BP		Lipid (stain + fibrate vs statin + placebo)		
	Intensive (SBP<120)	Standard (SBP<140)	Group A	Group B	
Intensive Glycemic Control (HbA1c<6%)	1178	1193	1383	1374	5128*
Standard Glycemic Control (HbA1c 7-7.9%)	1184	1178	1370	1391	5123*
	2362*	2371*	2753*	2765*	10,251

*Primary analysis compares marginals for main effects

ACCORD: Primary Outcome

- **Composite CVD outcome**
  - Nonfatal MI, nonfatal stroke, CVD death
  - Same outcome for all 3 questions
  - Adjudicated by blinded committee
- **Statistical power**
  - Glycemia: 89% power to detect 15% effect
  - BP: 94% power to detect 20% effect
  - Lipids: 87% power to detect 20% effect

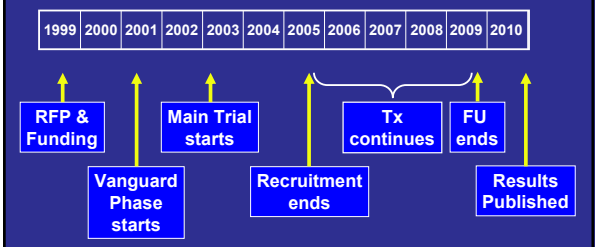
ACCORD: Secondary outcomes analyzed by randomized group

- Other cardiovascular outcomes - heart failure, need for revascularization
- Nephropathy
- Eye disease
- Neuropathy
- Health-related quality of life
- Cost-effectiveness
- Cognitive function

Different Treatment Strategies for Intensive and Standard Glucose Groups

- Compared with the standard group, the intensive group has:
  - Lower HbA1c goal (<6% vs 7-7.9%)
  - More frequent clinic visits
  - Point of Care HbA1c measures
  - Greater use of multiple medications
  - More likely to need insulin
  - SMBG guided therapy w/ greater SMBG frequency (2-8/day vs 1-3/day)

ACCORD: Timeline



Studies in Children: School and Community-based

Epidemiologic /Observational Identify potential risk factors, influences, and modifiers	RCT to determine *efficacy* of risk factor change	Community trials of intervention *effectiveness*	Community studies of *dissemination & translation* approaches
• NGHS	• DISC	• GEMS • Pathways • TAAG • CATCH • M-SPAN • SPARK	

Girls Health Enrichment Multi-site Studies (GEMS) (1999-2006)

- To develop and test obesity prevention interventions in high-risk African-American girls
- 8-10 years old at start
  - Phase 1 (1999-2002):
    - 4 studies; formative research and pilots
  - Phase 2 (2002-2006): 2 clinical trials
    - Primary outcome: BMI at 2 years
    - Parent/daughter evening sessions at community centers for diet and physical activity
    - Dance classes after school plus TV reduction

GEMS Pilot Studies' Results Overview—BMI & Diet

	Baylor	Minnesota	Memphis Child	Memphis Parent	Stanford
BMI, kg/m²	-	-	+	+	+
kcal	+	+	+	+	-
% fat	+	+	+	+	+
F&V, svg	+	-	+	+	
Water, svg	+	+	+	-	
Sweetened beverage, svg	+	-	+	+	

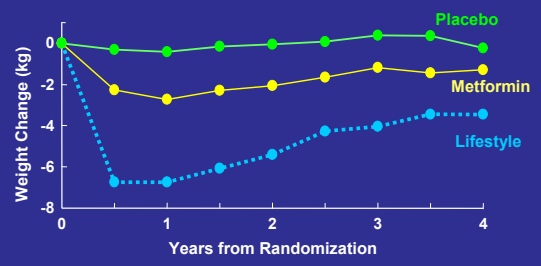
+ Indicates a difference in the desired direction
- Indicates a difference opposite to the desired direction

Ongoing Research in Children

- Trial of Activity for Adolescent Girls (2000-2007). A multi-center trial to reduce the age-related decline in physical activity in middle school girls by implementing a school- and community-based intervention.
- Twenty-four active Investigator-initiated grants related to childhood obesity and healthy lifestyles.

Lifestyle intervention reduces weight in overweight/obese pre-diabetic Individuals

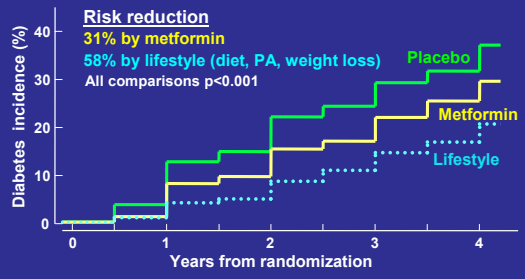
Diabetes Prevention Program (DPP), 3,234 pts with IGT



(DPP Research Group, *NEJM*, 2002)

Lifestyle intervention reduce diabetic risk in individuals with impaired glucose tolerance

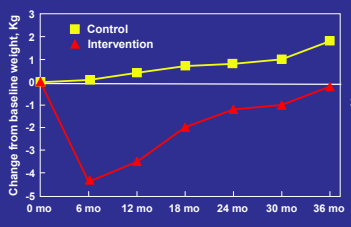
Diabetes Prevention Program (DPP), 3,234 ppts w/ IGT



DPP Research Group, *NEJM*, 2002

Counseling intervention results in weight loss, improved BP, and reduced HTN in overweight prehypertensive individuals

Trials of Hypertension Prevention II
n=2,382 pre-hypertensive adults



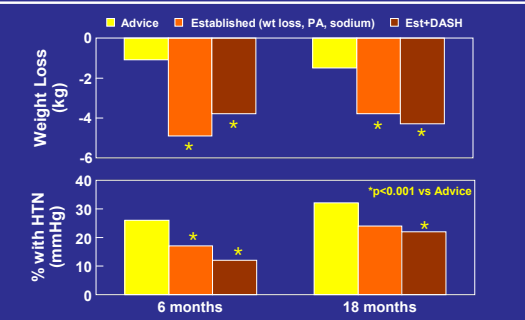
Net change intervention vs control

	BP (mm Hg)	RR of HTN
6 mo	-3.7***/-2.7***	0.58*
36 mo	-1.3**/-0.9*	0.81**

*p<.05 **p<0.01 ***p=0.001

Stevens et al., *Ann Intern Med*, 2001

Effects of Lifestyle Interventions on Weight and Hypertension Prevalence in Adults: the PREMIER Trial

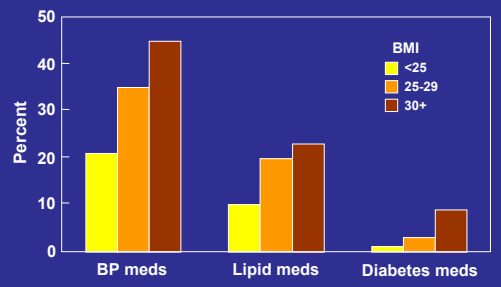


Appel et al. *JAMA* 2003 Elmer et al. *Ann Intern Med* 2006

Multi-Ethnic Study of Atherosclerosis (MESA)

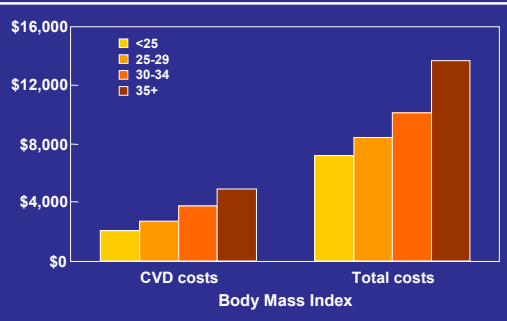
- Multi-center longitudinal study to identify prevalence and correlates or subclinical CVD and its progression
- 45-84 year old men and women without clinical CVD enrolled in 2000-2002; repeat exams at years 2, 5, 7, 10, 15, 20
- 38% white, 28% African American, 22% Hispanic, 12% Chinese participants
- n= 6,814 at baseline exam

MESA: Medication Use by BMI in White Women Aged 45-84, 2000-2002



Unpublished data.

Annual Medicare Charges for Inpatient and Outpatient Care in Men by Baseline BMI at Age 46 (1984-2002)



Adjusted for baseline age (mean=46 y), race, education, smoking; Daviglus et al. *JAMA* 2004; 2743-2749.

What Have We Learned?

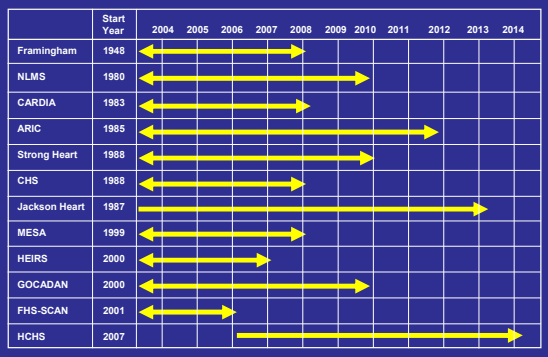
- Obesity/overweight increases CVD risk, both through and independent of, other CVD risk factors
- Moderate amounts of weight loss result in clinically meaningful effects on CVD risk factors in adults … 2-6 kg loss (5-10% body wt) + diet & PA changes→
  - 20% reduction HTN incidence (TOHP II)
  - 53% reduction HTN prevalence (PREMIER)
  - 47% reduction high LDL-C prevalence (PREMIER)
  - …that can reduce the need for medications
- Childhood weight is important for children's current health and is associated with future health

What Have We Learned?

- We <u>can</u> effectively help people lose weight
  - Diet and physical activity both important
  - Knowledge is not sufficient; Motivation is key
  - Behavioral approaches are effective:
    - Individual goal setting & Self-monitoring
    - Barriers identification & Problem-solving
- Effects of interventions on weight loss vary (some people maintain weight loss, many regain)
- Reducing or stopping intervention → some weight regain

Future directions: opportunities for intersection of the basic sciences with population based research

NHLBI Longitudinal Studies



Opportunities for Basic Science Research Within Population Studies:

- Preventing Overweight Using Novel Dietary Strategies (POUNDS Lost) Trial
  - RCT testing effects of four diets with differing macronutrient composition on weight loss and its maintenance in overweight or obese adults ages 30-70
  - Adipose tissue mini-aspirate on all (n=811)
  - Adipose tissue biopsies on subset (n=200)
  - Examine the effects of weight loss and fat cell size on adipose tissue gene expression (mRNA levels)

Missense Mutation in *LRP6* Gene Defines Metabolic Syndrome Risk Factors

***LRP6* Mutation in a Family with Early Coronary Disease and Metabolic Risk Factors**

Arya Mani, Jayaram Radhakrishnan, He Wang, Alaleh Mani, Mohammad-Ali Mani, Carol Nelson-Williams, Khary S. Carew, Shrikant Mane, Hossein Najmabadi, Dan Wu, Richard P. Lifton

A missense mutation in LRP6, which encodes a co-receptor in the Wnt signaling pathway, link a single gene defect in Wnt signaling to CAD and multiple CV risk factors

Mani A et al., *Science* 2007; 315: 1278

LRP6 Mutation Defines Early Coronary Disease and Metabolic Risk Factors: Comparison of Phenotypes

TRAIT	TRAIT+	TRAIT-	p value
LDL-C	170 +/-12	98 +/-5	6x10-6
TRIG	209 ± 71	68 +/-20	1x10-5
HDL-C	57 ± 8	56 +/-7	0.4
BMI	24.3+/-2.6	24.4 +/-1.6	0.13
SYST BP	168+/-21	116 +/-5	8x10-5
DIAS BP	100+/-14	81 +/-7	0.0025
F GLUCOSE	159 ± 43	80 +/-3	0.0001
DIABETES (Y/N)	11/4	0/5	0.005

Obesity, Risk Factors and CVD: Further Research is Needed

- Can we identify subgroups of individuals based upon genotype or biomarkers?
- Will a genetic understanding of obesity lead to a refined understanding of the etiology and pathophysiology of risk factor clustering and associated CVD?
- Will targeted treatments be safe and effective?
- Need for mechanistic studies

Obesity, Risk Factors and CVD: Further Research is Needed

- Integrate basic research findings into future clinical and population studies
- Major savings in healthcare costs could be achieved by successful prevention and intervention
- Cost-effectiveness of interventions is being examined; additional efforts are needed

Obesity, Risk Factors and CVD: Further Research is Needed

- Continue to integrate basic research findings into future clinical and population studies
- Major savings in healthcare costs could be achieved by successful prevention
- Cost-effectiveness of interventions is being examined; additional efforts are needed

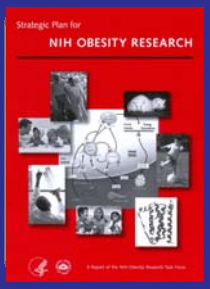
Strategic Plan for NIH Obesity Research

Goal:

- Maximize collaboration among 19 NIH Institutes and Centers
- Capitalize on their expertise and interest

Emphasizes research toward preventing and treating obesity:

- Lifestyle modification
- Pharmacologic, surgical, or other medical approaches
- Breaking the link between obesity and its associated health conditions
- Cross-cutting research topics, including health disparities



NHLBI support of new investigators