Introduction to the Principles and Practice of Clinical Research

APPLICATIONS OF HEALTH DISPARITIES RESEARCH
NIH Clinical Center

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Irene Dankwa-Mullan, MD, MPH
Acting Director, Division of Scientific Programs
NIMHD

Outline of Presentation

• Define Health Disparities
• Conceptual and Methodological Issues in Health Disparities Research
• Factors Contributing to Health Disparities
• Current Perspectives in Health Disparities Research
• Applications of Health Disparities Principles and Concepts in Clinical Research

Mission
NIH’s mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.
Healthy People 2020

Overarching Goals

1. Attain high-quality, longer lives free of preventable disease, disability, injury, and premature death;
2. Achieve health equity, eliminate disparities, and improve the health of all groups;
3. Create social and physical environments that promote good health for all; and
4. Promote quality of life, healthy development, and healthy behaviors across all life stages.

PART 1

What are Health Disparities?

Research in Population Health

Population health research examines the health outcomes of a group of individuals, including the distribution of such outcomes within the group.

Research approaches include metrics of health outcomes, patterns of health determinants and policies and programs that link these two.
Health Disparities Terminology

- **Health Disparities**
- **Variations**
- **Inequalities**
- **Inequity**
- **Age**
- **Disability status**
- **Gender**
- **Geography**
- **Race / Ethnicity**
- **Religion**
- **Socioeconomic Status**
- **Sexual Orientation**

U.S. Healthy People 2020

U.S. Health and Human Services

Healthy People 2020: A health disparity is a "particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage.

Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental status; cognitive, sensory or physical disability; sexual orientation or gender identity; geographic location or other characteristics historically linked to discrimination or exclusion.

Health Disparities Research

A broad multi-faceted field that includes basic, applied, clinical, social and behavioral research, as well as translational research addressing significant disparities in the overall health status, rate of disease incidence, prevalence, morbidity, mortality or survival rates – observed in a population or population subgroup.

It includes the causes of such disparities and methods to identify, prevent, diagnose and treat such disparities, with the eventual goal to addressing causes and implementing solutions.
Epidemiology and Health Disparities Research:

Epidemiology = study of the distribution and patterns of health-events, health-characteristics and their causes or influences in well-defined populations.

- Cornerstone method of public health research and practice,
- Helps inform policy decisions and evidence-based medicine by identifying risk factors for disease and targets for preventive medicine and public policies.

Health Disparities Terminology

Social Disparities in Health – disparities in health that is patterned by socioeconomic status (includes race)

Racial and/or Ethnic disparities in health – Divergence in health outcomes that are patterned by race and ethnicity

Biological determinants and health disparities – differential distribution of risk variants in certain populations that put them at unique susceptibility or protection.

Health Disparities Terminology

Healthcare disparities
- Differential access to health care and services
- Differential quality of health care
  - Medical uncertainty and variation
  - Lack of inclusion in clinical trials and evidence-base
  - Discrimination, bias and stereotyping

Resulting in differential health outcomes
- Excludes patient preferences
Healthcare Disparities

In Healthcare, quality, access, utilization and clinically appropriate care is important.

Determinants of Healthcare Disparities

Social Determinants of Health

The social determinants of health are the circumstances in which people are born, grow up, live, work, and age, as well as the systems put in place to deal with illness. These circumstances are in turn shaped by a wider set of forces: economics, social policies, and politics.

The social determinants of health are mostly responsible for health inequities - the unfair and avoidable differences in health status seen within and between countries.
Social Health

Person’s capacity to fulfill their potential and obligations, the ability to manage their life with some degree of independence (despite a medical condition), and the ability to participate in social activities including work.

Health in this domain can be regarded as a dynamic balance between opportunities and limitations, shifting through life and affected by external conditions such as social and environmental challenges.

### Social Health

- Financial health
- Social networks and inclusion
- Community health and cohesion
- Civic engagement
- Food security; access to healthy foods
- Safe neighborhoods to play
- Safe working conditions
- Access to educational opportunities
- Etc.

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**PART 2**

Determinants of Population Health and Health Disparities
Determinants of Population Health

Health Disparities at the Population Level

Part 3
Conceptual and Methodological Issues
Issue #1: Defining when a health difference is a disparity
Moral concern about the differences in health status, health outcomes. Value judgments are often made.

<table>
<thead>
<tr>
<th>HEALTH Disparities</th>
<th>AXIS Age</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Socioeconomic Status</td>
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<td></td>
<td>Sexual Orientation</td>
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</table>

Health Disparities Terminology

Language of Health Disparities

Health Inequity

Is it fair that:
Poor people die younger than rich people.

• It is an unavoidable fact of life.
• Economics should not affect well-being
• People are responsible for their own well-being
• If people really want access to high quality care and preventive services, they can get it.

Language of Health Disparities

Health Inequity

Is it fair that:
Low SES class infants have lower birth rates.

• Preventing lower birth weight among low SES class infants should be a top priority for society
• Low birth weight may be an indicator of irresponsible parenting
• Babies are innocent, and their health should not be determined by the social class of their parents
• It will cost society too much to prevent all undesirable birth outcomes
Language of Health Disparities

Health Inequity

Is it fair that:
Smokers get more lung cancers than non-smokers.
  • Smoking is a choice
  • Smokers are victims of the tobacco industry
  • If people were not so stressed, they would not smoke as much
  • Smokers understand the health risks of smoking and should be held accountable for their behavior

Health Disparities Definitions

Health Inequities

Systemic and unjust distribution of determinants of health: i.e. social, economic, and environmental conditions needed for health:
Unjust access to quality education, healthcare, housing, transportation and other resources (e.g. grocery stores, playgrounds, walking spaces)
Unequal employment opportunities and income
Discrimination based upon social status and other factors

Issue 2: Unit of Analysis – Between Population Groups

Reference Group or Comparison Group

Measuring Health Disparities
Reference Group or Comparison

The choice of the reference group will affect the size of the disparity.

Measuring Health Disparities

Reference Group or Comparison

Measuring Health Disparities

Quantifying the Health Disparities

Issue # 3: Size of population, changing demographics

Population Changes over time

Does it matter whether we are measuring health disparity at a single point in time, or over time?

- Demographic changes
- Immigration changes
- Environmental changes

PART 3
Current Perspectives in Health Disparities Research
Social Disparities in Health

Higher Income, Longer Life

Social Disparities in Health Outcomes

Lower Income is Linked With Worse Health

Racial or Ethnic Differences in Health Regardless of Income

Annual or ethnic disparities do not simply reflect differences in income. Racial or ethnic disparities are the by-product of poor or fair health are seen within each income group. Both income and racial or ethnic group matter.
Examples of health disparities

Life Expectancy at Birth, by Race* and Sex, 1970–2006
Source: U.S. Centers for Disease Control and Prevention, National Center for Health Statistics

Biological Health and Stress

Allostatic load is a multisystem construct theorized to quantify stress-induced biological risk.

Differences in allostatic load may reflect differences in stress exposure and thus provide a mechanistic link to understanding health disparities.
Physical Health and Allostatic Load

Two categories of biomarkers:
Primary Mediators comprises the substances the body releases in response to stress (e.g. Epinephrine, norepinephrine)

Secondary Effects / biomarkers comprises the results from the actions of primary mediators (e.g. elevated BP, HbA1c, lipids)

Variables Used in the Allostatic Load Literature

Commonly used variables:
Physiologic stress response hormones; e.g. cortisol, epinephrine and norepinephrine, dopamine, insulin-like growth factors, Dehydroepiandrosterone sulphate (DHEA-s)

Metabolic markers; e.g. glycosylated hemoglobin (HbA1c), fasting and postprandial glucose, and waist:hip ratio

Cardiovascular variables; e.g. systolic and diastolic blood pressure, HDL and total cholesterol

Inflammation markers; e.g. albumin, C-reactive protein, interleukin-6, tumor necrosis factor

Measures of organ function; e.g. creatinine function, homocysteine

Cumulative Biological Risks: Metabolic Score* by Education

Metabolic Score = sum (glyco. Hemoglobin, HDL and total cholesterol, waist:hip ratio)

Cardiovascular Score* by Education

Cardiovascular Score = sum (Systolic and Diastolic BP, resting heart rate)
Seeman et al, Soc Sci & Med

Biological Determinants of Health

1. Endogenous
   (a) Genetic
   (b) Immunological defenses, including nutritional status
   (c) Intrinsic biological attributes, age, sex
   (d) Epigenetic – determined largely by biological and physical environmental challenges (which may be passed on from generations)

2. Exogenous

Biological Determinants of Health

1. Endogenous

2. Exogenous
   Pathogens (harmful) that cause pathological processes or diseases
**Developmental Origins of Health and Disease**

**Concept:** biologic capacity of normal developing organisms to be durably changed by environmental exposures without change in the inherited genome

**Process:** 'developmental programming'

**Exposures:** nutrients, O2, chemicals, toxins

**Pathways:**
- Δ organ structure (permanent)
- Δ cell/organ function (± reversible)
- Δ regulatory system setpoints

**Impact:** Vulnerability to development of chronic disease in later life

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**Key Points**

Developmental programming

- first recognized because it created socioeconomically-based health disparity

- is a major mechanism by which
  - Socio-economic/psychosocial stressors become biologically embedded within a population
  - developmentally-based health disparities can be transmitted to future generations

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**Biology of Developmentally-Programmed Health Disparities**

*Courtesy: S. Bagby, MD*
Life Course Epidemiology: Two models

Cumulative risk model
- Chronic stressors can lead to cumulative dysregulation or damage across lifecourse.

⇒ Critical period model
- Early life experiences can durably modify biology by changing development.
- These modifications interact with later behaviors or exposures to influence health.


Altered Organ Structure/Function

“Critical Windows” of Organ Development

Brain

Placenta

Pancreas (insulin)

Kidney (functional units)

Early Heart

Heart cell maturation

Embryo → Fetus → Birth

Time from Conception

Courtesy: S. Bagby, MD
Mechanisms of Fetal Programming

Structural Deficits → ↓ # Functional Units

<table>
<thead>
<tr>
<th>Organ</th>
<th>Change</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>↓ Nephron #</td>
<td>HTN, renal risk</td>
</tr>
<tr>
<td>Pancreas</td>
<td>↓ Islet β cell #</td>
<td>△ Insulin secretion</td>
</tr>
<tr>
<td>Muscle</td>
<td>↓ muscle mass</td>
<td>↓ Basal met rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Exercise capacity</td>
</tr>
<tr>
<td>Heart</td>
<td>↓ myocyte #</td>
<td>↑ Risk CHF</td>
</tr>
<tr>
<td>Liver</td>
<td>↓ lobule, cell #</td>
<td>? △ lipid metabolism</td>
</tr>
<tr>
<td>Vascular</td>
<td>↓ microvasc dens</td>
<td>↑ vasc resistance, ischemia risk</td>
</tr>
</tbody>
</table>

Developmental Origins of Disease

Asymmetric Growth Restriction

- Thin (Wt:Ht ratio)
- Blood flow redistribution
  - ↓ kidney, liver, pancreas
  - ↓ abdom'l girth, Heart/brain 'sparing'
- Low arm circumference
  - ↓ muscle mass
- Can occur without low birth weight

Courtesy: S. Bagby, MD

Mechanisms of Fetal Programming

Time Course of Renal Development

<table>
<thead>
<tr>
<th># Glom (% Max)_{100}</th>
<th>Human</th>
<th>Rat or Pig</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>5-35 wks</td>
<td>5-35 wks</td>
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</table>

Courtesy: S. Bagby, MD
New Nephrons Form in Concentric Layers during Gestation

Condensing Mesenchyme → Comma Shaped Bodies → Glomeruli

Outer Nephrogenic Layer
Branching Morphogenesis → Nephrogenesis

In Term Births:

Birth Weight Predicts Nephron Number

Δ ≈ 230,000 nephrons per kg increase in birth weight

Hughson et al, Kid Internat (2003) 63, 2113

What Conveys Risk of HTN-Renal Disease in Low Birth-weight Offspring?

Low Nephron Number?


Nephron Dosing

Brenner Hypothesis1,2

Body Mass
Nephrons
Risk of HTN & Renal Disease

Courtesy: S. Bagby, MD
Mismatch

END STAGE RENAL DISEASE (ESRD)
High Cardiovascular Risk
Chronic Kidney Disease (CKD)
Reduced GFR (late stage)
HTN
↓ Salt Excretion
Progressive nephron loss;
Fewer and fewer functional nephrons

Focal Glomerular Sclerosis

Courtesy: S. Bagby, MD

 Fewer Nephron Units Promotes Hypertension

IN
BP
OUT

IN
OUT

How important are developmental and epigenetic processes to U.S. disparities between “racial” and ethnic groups?
Trends in Low Birth Weight (LBW)

Trends in Very Low Birth Weight (VLBW)

Major US health disparities:
Disproportionate burden of poor health outcomes among individuals experiencing low SES and African Americans

Early life
- Prematurity
- Low birth weight
- IUGR

Adulthood
- Heart attack
- Stroke
- Diabetes
- Hypertension
Developmental Origins of Adult Health

Environmental Stressors

Activation of the HPA axis in stressful intrauterine conditions

Developmental response

Overexposure of the fetus to glucocorticoids

- Under-nutrition
- Over-nutrition
- Exposure to toxins

Biological Changes

Long-term chronic illness and effects

Low SES, Racism, Discrimination, Nutrition etc.

Courtesy of C. Kuzawa PhD


Incident ESRD patients; Rates by age & Rates by race/ethnicity (1980 – 2004)

Incident ESRD patients, rates by age adjusted for gender & race, rates by race & ethnicity adjusted for age & gender. For Hispanic patients, no data for race, beginning in 1996. The first full year after the April 1995 introduction of the revised Medical Evidence form, which contains more specific questions on race & ethnicity.

MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis

Genetic variation at the MYH9 locus substantially explains the increased burden of FSGS and hypertensive ESKD among African Americans.

Disparities in Chronic Kidney Disease and ESRD

A risk allele for focal segmental glomerulosclerosis (FSG) in African Americans is located within a region containing APOL1 and MYH9

2010 International Journal of Nephrology

- Found APOL1 variants associated with non-diabetic glomerular disease in African American populations
- Stronger associations than with European Americans
- Higher prevalence of this gene than anticipated in the population

Proposed pathogenesis of MYH9-associated nephropathy.
Coronary Heart Disease Outcomes, by Race and Sex in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort

Health Disparities

**Thesis 1:**
An individual's biological health embodies exposures arising from their societal, political, cultural and environmental context, thereby producing population rates and distributions of health.

- Poverty and adverse life effects have harmful effects on health
- Psychosocial stressors are socially patterned

Health Disparities

**Thesis 2:**
Social stratification and inequalities

- Arises from and reinforces unequal distribution of resources
- Linked with social disparities – education, income, employment etc.
- Creates the persistent social gradient in a number of indices including health status, clinical encounters, access and health outcomes.
Health Disparities

Thesis 3:
Differences in population health, that creates health disparities are the result of socially patterned gradients in health, mediated by physiology, behavior, psychosocial pathways and gene-environment expression, that affect the development, growth and regulation of our body’s biological systems, organs, and cells, culminating in disease risk, morbidity or mortality.

Elements that are desirable in conducting health disparities research

A scientifically rigorous and transparent strategy for measuring health disparities
• Across multiple dimensions of the population
• Across multiple health indicators
• Across time

Appropriate Data Sources

Review of the relevant dimensions of health that is pertinent to the individual or community
• Social environment
• Intervening variables, e.g. life course trajectories

National Institute on Minority Health and Health Disparities
www.nimhd.nih.gov

Irene Dankwa-Mullan MD MPH
dankwamullani@mail.nih.gov
301.402.1366