Webinar Series: Early Environmental Exposures to Hazardous Pollutants/Chemicals and their Associations with Chronic Disease

Webinar 2:
Focus on Endocrine Disruption and Obesogens
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Webinar 1: Introduction to the Scoping Review

**Webinar 2: Focus on Endocrine Disruption, Obesogens and Diabetogens**

- Recap of Main Findings
- Terminology, Prevalence and Incidence, Importance
- Epigenetic/Environmental Basis of Disease; Implications of Endocrine Disruption Science
- Obesity Risk Factors
- Obesogens and Diabetogens

Webinar 3: Policy Implications
Scoping Review: Main Findings

• Increasing evidence of associations
• Early exposures, despite uncertainty, should be seen as chronic disease risk factors
• Developmental origins (DOHaD) concept – very solid evidence and rapidly expanding to include early life exposures
• 3+ decades of complex and interrelated changes to consider
• Continuum of shared, well-known risk factors across multiple chronic diseases
  • Primacy of social determinants of health
  • Environmental risk factors likely also shared
• Wide range of chemicals and pollutants implicated
Definitions

Obesity and Overweight

- Obesity: Body Mass Index above 30 kg/m²
- Overweight: BMI between 25 and 30
- Calculation from height and weight; different calculation for children
- Sample calculator: http://www.cdc.gov/healthyweight/assessing/bmi/index.html

Diabetes (Type 2 – 90% of cases)

- Chronic condition; body does not produce enough and/or does not properly use its own insulin (intolerance/resistance).
- Result: chronic hyperglycemia (high blood sugar), in turn adversely affecting how the body metabolizes carbohydrates, fats, and proteins.
- Insulin: hormone produced in the pancreas that enables cells to absorb glucose and transform it into energy. Also involved in blood vessel elasticity, cognition, and whole-body homeostasis.


- 3 out of 5 of: increased waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol levels, elevated blood pressure, and elevated fasting glucose levels
Obesity and Type 2 Diabetes - High Prevalence and Rising Incidence

**Type 2 Diabetes**
- Projected for 2012 - ~2.8 million Canadians
- Annual increase of ~6% and overall increase of ~25% since 2007.
- Biggest ↑ is in young adults.
- **Higher prevalence among the poor** (low income 4x > highest income; First Nations 3 to 5X > gen’l pop’n)

**Obesity**
- Similar increase; approx. 25% of pop’n esp. among children, and much higher in First Nations
- If include both overweight and obesity – over 50% of the population

**Metabolic Syndrome/”pre-diabetes”**
- Approx. 25% of pop’n
Common Risk Factors Across Multiple Chronic Diseases

Continuum of common and overlapping risk factors for:

- Obesity
- Metabolic Syndrome
- Type 2 Diabetes
- Cardiovascular Disease
- Vascular Dementia
- Alzheimer’s Disease (Type 3 or “diabetes of the brain”)

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Diabetes and Obesity - Greater Risk of
Death and Disease

Adults with Type 2 Diabetes have greater risk of:
- mortality (2x)
- hypertension, heart attack or stroke (3x)
- heart failure (4x)
- chronic kidney disease (6x)
- lower limb amputations (19x)
- Alzheimer’s disease and vascular dementia

Adult obesity brings greater risk of:
- mortality (2.5X)
- cardiovascular disease (4X)
- Type 2 Diabetes (5X)
- hypertension, gall bladder disease, some cancers
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Timing of in utero nutritional deprivation is associated with different later-life disease outcomes

DOHaD recap: inappropriate adaptation to early-life stresses

*In utero* stress (nutritional deprivation or chemical exposure):

- Epigenetic mechanisms: mediators of later-life expression of these early life events
- **Environmental sensitivity of epigenome is adaptive mechanism** – developing organism adjusts its metabolic and homeostatic systems to suit anticipated postnatal env’t
- Latent diabetes risk from altered gene expression in key organs and metabolic processes
  - Response to environmental stimulus is a shift in the developmental path to achieve survival or reproductive advantage
  - If mismatch between prenatal and postnatal environment: latent risk of obesity, etc. is “built-in”
Epigenetic/Environmental Basis of Disease

“Two Sides of the Same Coin”


Normal Tissue Cell

In utero nutritional deprivation/Endocrine Disrupting Chemicals

Normal Differentiating Cell (Development)

Altered Gene Expression (persists due to epigenetic marks)

Altered Proteins and/or Protein Concentrations

Latent Disease/Dysfunction
Hormone Functions

- Reproduction and sexual differentiation
- Development and growth
- Maintenance of the internal environment
- Regulation of metabolism and nutrient supply
Fat/Adipose Tissue is Active Endocrine Tissue

Previously established functions
- Glucose uptake and conversion
- Lipogenesis and lipolysis
- Beta oxidation of fatty acids

Newly accepted functions
- Role in pathogenesis of diabetes, cardiovascular disease, and cancer
- Endocrine regulation of energy balance

Leptin
Adiponectin
IL-6

ADIPOSE TISSUE

INTESTINE (distal ileum, colon)

Peptide YY
GLP-1

Stimulates orexigenic system
Inhibits anorexigenic system

Ghrelin

Stomach

PANCREAS

GLUCOSE

Insulin

Insulin

Suppresses glucagon release

EACH

Enhances glucose-induced insulin secretion and suppresses glucagon release

Regulates
- Food intake
- Metabolism
- Energy expenditure

BRAIN (hypothalamus)

Stimulates orexigenic system
Inhibits anorexigenic system

Leptin
Adiponectin
IL-6

Glucose uptake and increases insulin sensitivity

Contributes to insulin resistance

SKELETAL MUSCLE

LIVER

GLUCOSE
Adipose Tissue During Development

Adipose Tissue:

- dynamically regulates energy expenditure, appetite, food intake and metabolism.
- significantly involved in growth and development
- endocrine signaling pathways permanently established during prenatal and perinatal development.
- Extension of DOHaD concept:
  Assoc. between restricted fetal nutrition an latent obesity and metabolic syndrome

Exp’tl studies of EDCs known or suspected to act as obesogens during same prenatal and perinatal periods via the same/similar pathways or epigenetic mechanisms
Similarities Between Hormones and Endocrine Disrupting Chemicals (EDCs)

Both act at extremely low doses

Hormones

- picomolar to nanomolar range
- Low doses allow huge number of hormonally active molecules to co-exist in circulation
- Animal data and human twin studies: fetal endocrine system is permanently affected by exposure to low doses of hormones

EDCs

- nanomolar to micromolar, some at picomolar range
- Biomonitoring data confirm population-wide exposure (usually at parts per billion) to hundreds of chemicals, incl. EDCs
- Epidemiological studies show associations between disorders in humans and EDCs at prevailing exposure levels

During development, both are capable of altering organ morphology, physiology, and reproductive development
Similarities Between Hormones and Endocrine Disrupting Chemicals (EDCs)

Non-monotonic dose-response curves

Hormones

• well-established in endocrinology; used as basis for clinical interventions
• Explains why hormones can act at very low doses

EDCs

• NMDRCs once thought unusual, now confirmed as very common
• High dose cannot predict low dose; cannot predict a threshold

Key Differences

Three phases:
Free, Bioavailable, Inactive
Acts as buffering system

Most is physiologically active
No natural buffering
Even low concentrations can disrupt natural hormones

Endocrine-Disrupting Chemicals

• Diverse pathways that are highly conserved across species
• Can be modelled *in vitro* and *in vivo*
• Timing matters, long latency
• Effects can be transmitted to future generations

**Strong evidence:**
• Adverse reproductive effects (infertility, cancers, malformations)

**Mounting evidence:**
• Effects on thyroid, neuroendocrine, and metabolic systems as well as on insulin and glucose homeostasis

*Endocrine Reviews;* 30(9):293-342. 2009
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– **Obesity Risk Factors**
– **Obesogens and Diabetogens**

Webinar 3: Policy Implications
Risk Factors for Obesity

- Diet and exercise – often the primary focus
  - Sedentary lifestyles
  - changes in built env’t, food system and food composition
- Many other RF are equally plausible.
- A similar body of evidence exists for at least 10 additional risk factors. Similar evidence in terms of data for:
  - Statistical trends over time
  - Human studies, both cross-sectional and longitudinal, including clinical and epidemiological
  - Animal evidence, e.g., to indicate mechanism of action
  - Epidemiological studies supported by animal experimental data.
  - Epigenetic research about DOHaD
  - Etc.

Multiple interactions across all

Risk Factors Contributing to Pop’n-Wide Increase in Obesity

1-10: evidence for link to obesity is incomplete but as plausible as link to diet and exercise (Keith, 2006)

1. Endocrine-disrupting substances
2. Sleep debt
3. Less variability in ambient temp.
4. Decreased smoking
5. Pharmaceutical iatrogenesis
6. Changes in distrib’n of ethnicity and age
7. Increasing gravida age
8. DOHaD intergenerational effects
9. Greater BMI assoc’d with greater repro. fitness yielding selection for obesity-pre-disposing phenotype
10. Assortative mating effects

Human Adenovirus 36 also correlates with rise in obesity (more limited evidence)
Stress and poverty well known to be correlated with obesity
Fructose consumption – similar increase over past 30+ years
Gut microbiota composition and likely interactive with exposure to EDCs
Chemicals Suspected as Obesogens/Diabetogens

- Diethylstilbesterol (DES)
- Bisphenol A (BPA)
- Phthalates
- Tributyltin
- Organophosphate pesticides
- Persistent Organic Pollutants (POPs) including polybrominated diphenyl ethers (PBDEs), organochlorine pesticides, PCBs, dioxins, polyfluoroalkyl compounds

Above are: pharmaceuticals, consumer products, or banned but still circulating substances (often contaminating food)

High-fructose diet assoc’d with:
- higher blood pressure and fasting glucose
- insulin resistance and inflammatory factors that contribute to heart and vascular disease.
- Lower levels of cardiovascular protectors such as such as HDL cholesterol and adiponectin (hormone involved in metabolism including glucose regulation)
Evidence in Adults

Recap from Summary in 1st Webinar:

- **Air pollution** (*Causal relationship between air poll’n and CVD*): systemic inflammation and oxidative stress — risk factors for elevated blood pressure, insulin resistance, and abnormal blood lipids.

- **Lead** (*Strong evidence of association*): hypertension

- **Bisphenol A** (*animal data and limited epidemiological/human population studies*): altered insulin signaling

- **Phthalates** (*animal data and limited epi. evidence*): links to measures of obesity and insulin resistance

- **Organophosphate pesticides** (*limited epi., some animal data*): links to altered insulin signaling

- **POPs** (organochlorine pesticides, dioxins, PCBs) (*epi. and animal data*): altered insulin signaling, elevated rates of T2D
Epidemiological Evidence Prompted Animal Research

- Disruption of metabolic homeostasis through endocrine pathways with **greater risk when exposure occurs in utero or perinatally**
- Progression of DOHaD research
- Fetal under-nutrition and over-nutrition both relevant – former resulting in later life obesity, etc. whereas latter resulting in neuroendocrine responses that program fat cell development and appetite regulation
  - Implications of latter: childhood and adolescent obesity and thus ability to lead to intergenerational obesity
Example: Bisphenol A

Animal data

• Influence on adipose tissue and/or glucose metabolism
• Prenatal and perinatal BPA exposure associated with permanent alteration of insulin metabolism.
  – Stimulation of glucocorticoid receptors (GR) → increased fat accumulation in differentiating fat cells
  – ER pathways → modulation of glucose transport in fat cells
  – Suppression of adiponectin (affecting insulin sensitivity and resistance)
  – Results are inconsistent – depend on route of exposure, sex, and species
Example: Tributyl Tin

Animal data

- Developmental obesogen
- Action through nuclear receptor signalling
  - PPARγ (master regulator of fat cell development) and RXR receptors
- Single prenatal exposure to tributyltin:
  - premature accumulation of fat, and greater size of fat tissues relative to body mass
  - Epigenetic mechanism here is clearly established
- Puberty and pre-puberty exposure:
  - Increased body weight gain
  - Hepatic steatosis (fatty liver)
  - Hyperinsulinemia (elevated insulin circulating in the blood)
  - Hyperleptinemia (appetite regulating hormone produced by adipose tissue)
Example: Persistent Organic Pollutants

- Can’t generalize effects to entire classes of chemicals, mechanisms not always clear
- POPs can affect the metabolic and endocrine function of adipose tissue (AT)
- Diverse mechanisms mediated through nuclear receptors+ (inflammation, disrupted metabolism, altered cellular differentiation)
- Complex, multiple, and dose-dependent effects (indication of NMDR curves)
- Evidence of effects in adults as well as developmental obesogenic effects
- Result is excess lipids (and proinflammatory state) in AT
- Obesity itself alters AT structure and function (excess lipid accumulation and macrophages/inflammatory marks)
Obesogens and Diabetogens

Chemicals that Promote Obesity by:

• Increasing the # of fat cells (and fat storage into existing fat cells).
• Changing the amount of calories burned at rest.
• Altering energy balance to favour storage of calories.
• Altering the mechanisms through which the body regulates appetite and satiety.

“Diabetogens”: Chemicals associated with altered insulin signaling
Diverse Mechanisms for Obesogenic Effects

- Mediated by metabolic sensors on nuclear or membrane hormone receptors
- Mediated by sex steroid dysregulation
- Interaction with neuroendocrine signalling control response to nutritional changes
  - Thyroid gland involvement
- Effects within glucocorticoid signalling
- Across all – greater effects from early life exposure
Can we know what proportion of the obesity epidemic is caused by chemicals?

Probably not
(but, never say never – see Bellinger 2012 *EHP* 120(4): 501-7)

What we do know:

• Endocrine disrupting chemicals operate by diverse mechanisms
• Increasing but incomplete body of knowledge showing associations with obesity and diabetes
• Across all – greater effects seen from early life exposure and effects are permanent
• Likewise for some drugs and foods → alterations in dev’t, physiology, metabolism, and behaviour that favours the storage of excess calories as fat
• **Metabolic changes from obesogens are superimposed on current trends in other obesity risk factors**
• Poverty increases and compounds risk
Scientists Seek Policy Change

Endocrine Disrupting Chemicals and Public Health: Endocrine Society Statement of Principles

Assessing Chemical Risk: Societies Offer Expertise to Regulatory Agencies (8 Mainstream Scientific Societies)

Testing protocol for new chemical design

Designing endocrine disruption out of the next generation of chemicals, 15: 181-98. 2013

153(9):4097-4110. 2012

331: 1136. 2011


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