Epidemiology of Childhood Overweight and Obesity

Is there a role for factors other than the ‘usual suspects’?

NIEHS Workshop, January 23, 2007

Overview

- Prevalence and time trends of childhood obesity and metabolic syndrome
- Review of ‘established’ risk factors
- Alternative hypotheses -- endocrine disruptors
- Limitations of epidemiologic studies
- Future directions
Definitions of childhood obesity

- Definition straightforward in adults
  - Overweight $\Rightarrow$ body mass index (BMI) $>25$-29.9 kg/m$^2$
  - Obese $\Rightarrow$ BMI $\geq 30$ kg/m$^2$  

- In children, based on percentiles
  - 'At risk for overweight' $\Rightarrow$ BMI $> 85^{th}$ percentile for age, sex and height, based on CDC growth charts
  - 'Overweight' $\Rightarrow$ BMI $> 95^{th}$ percentile

- Inconsistent definitions across studies

- BMI has poor sensitivity and specificity for level of body fat; measures of central obesity may be preferable

Prevalence of childhood overweight and obesity, 1971-2004, by racial/ethnic group, U.S.

http://www.cdc.gov/nccdphp/dnpa/obesity/childhood/prevalence.htm
Figure 1. Trends in Child and Adolescent Overweight

Prediction of BMI distribution in adults, 2008

Prediction of BMI distribution in adults, 2008

The entire curve has shifted


Trends in overweight in adolescent boys, aged 12-19, 1988-2004
Trends in overweight in adolescent girls, aged 12-19, 1988-2004

Obesity trends by Socioeconomic level, NHANES surveys
Global increases in the prevalence of childhood obesity

Summary of obesity statistics

- In U.S., “epidemic” didn’t start until the early 1980’s
- Racial and ethnic disparities, particularly in females
- Shift in entire BMI distribution, not only in the right tail
- Global increases in obesity have occurred
- Increased trends in other countries started later than in the U.S.
Metabolic syndrome

- Linked to high risk of Type 2 diabetes and cardiovascular disease
- Defined by 3 or more of following abnormalities:
  - Elevated triglycerides
  - Low HDL
  - Elevated fasting glucose
  - Large waist circumference
  - Elevated systolic blood pressure

Changing prevalence of metabolic syndrome in adolescents, 1988-2000

- Overall prevalence of 3 or more abnormalities increased from 9.2% to 12.7%
- Prevalence of syndrome in overweight teens was 38.6% in 1999-2000 survey
- Prevalence in non-whites increased more sharply than in whites (3 fold increase in blacks)
- Waist circumference (above 75% in NHANES 3) increased from 25% to 34%

Ferranti SD et al; Clinical Chemistry, 2006
Critical periods of increased risk for development of obesity

- Prenatal
- Adiposity rebound
- Puberty/adolescence

- Childhood overweight and obesity strongly linked to adult overweight and obesity
- Therefore, early life prevention of obesity is critical—treatment is difficult and mostly ineffective
Critical periods of increased risk for development of obesity

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Complications of childhood obesity

- Psychosocial:
  - Poor self-esteem
  - Depression
  - Eating disorders

- Pulmonary:
  - Sleep apnoea
  - Asthma
  - Exercise intolerance

- Gastrointestinal:
  - Gallstones
  - Steatohepatitis

- Renal:
  - Glomerulosclerosis

- Musculoskeletal:
  - Slipped capital femoral epiphysis
  - Scoliosis
  - Forearm fracture
  - Flat foot

- Cardiovascular:
  - Dystipidaemia
  - Hypertension
  - Coagulopathy
  - Chronic inflammation
  - Endothelial dysfunction

- Endocrine:
  - Type 2 diabetes
  - Precocious puberty
  - Polycystic ovary syndrome (girls)
  - Hypogonadism (boys)

Ebbeling C et al, Lancet, 2002
Early life risk factors for development of overweight and obesity

- Genetic factors
- Maternal factors
  - Pre-pregnancy BMI
  - Pregnancy weight gain
  - Diet
  - Gestational diabetes
  - Smoking in pregnancy
- Pre- and perinatal factors
  - Low birth weight
  - High birth weight
  - Breast feeding (protective)

Childhood risk factors: ‘the usual suspects’

- Energy balance
  - Activity
    - Decreased physical activity
    - Increased sedentary behavior (TV etc)
  - Diet
    - Fast food intake
    - Increased portion sizes
    - Fat intake/type of fat consumed
    - Changing balance of carbohydrates vs. fat
    - Sugar sweetened beverages
    - High fructose corn syrup
- The ‘built environment’
- Social/demographic/family factors
Relationship between overweight and TV viewing

Limitations of current epidemiologic studies

- Mostly cross-sectional to date

- BMI is a proxy measure of obesity—misclassifies some individuals
  - Is central adiposity (waist circumference or waist to hip ratio) a better measure?

- Analytic challenges
  - What are the critical time periods for exposure?
    - Different risk factors operate during different time periods
  - Are risk factors independent of each other or interacting over the life course (in epi-speak, is there confounding or effect modification?)
Results from Avon longitudinal study, Reilly JJ et al, BMJ 2005

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>1.05 (1.03-1.07)</td>
</tr>
<tr>
<td>Maternal Smoking &gt;20/day</td>
<td>1.80 (1.01-3.39)</td>
</tr>
<tr>
<td>Parental obesity (both parents)</td>
<td>10.4 (5.11-21.32)</td>
</tr>
<tr>
<td>TV at age 3</td>
<td></td>
</tr>
<tr>
<td>≤ 4</td>
<td>1.00</td>
</tr>
<tr>
<td>4-8</td>
<td>1.37 (1.02-1.83)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>1.55 (1.13-2.12)</td>
</tr>
<tr>
<td>Sleep duration (hrs) at age 3</td>
<td></td>
</tr>
<tr>
<td>&lt;10.5</td>
<td>1.57 (1.23-1.99)</td>
</tr>
<tr>
<td>10.5-10.9</td>
<td>1.31 (1.02-1.69)</td>
</tr>
<tr>
<td>11-11.9</td>
<td>0.94 (0.71-1.25)</td>
</tr>
<tr>
<td>12+</td>
<td>1.00</td>
</tr>
</tbody>
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*all results adjusted for maternal education

Results from Avon longitudinal study, Reilly JJ et al, BMJ 2005

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<tr>
<th>Risk Factor</th>
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<tr>
<td>Std dev score for weight</td>
<td></td>
</tr>
<tr>
<td>Top quartile, 8 mos</td>
<td>3.03 (1.89-4.85)</td>
</tr>
<tr>
<td>Top quartile, 18 mos</td>
<td>3.71 (2.29-6.00)</td>
</tr>
<tr>
<td>Adiposity rebound</td>
<td></td>
</tr>
<tr>
<td>Late (&gt;61 mos)</td>
<td>1.00</td>
</tr>
<tr>
<td>Early (by 61 mos)</td>
<td>2.85 (1.53-5.33)</td>
</tr>
<tr>
<td>Very early (&lt;43 mos)</td>
<td>12.0 (6.01-24.03)</td>
</tr>
<tr>
<td>Catch up growth</td>
<td>2.21 (1.30-3.80)</td>
</tr>
<tr>
<td>Weight gain first 12 mos (per 100 gram increase)</td>
<td>1.07 (1.05-1.10)</td>
</tr>
</tbody>
</table>
What else might contribute to increases in childhood obesity?

- Sleep patterns
- Air conditioning and heating
- Increased medication use
- Increased stress
- Viruses
- Endocrine disrupting chemicals


Central adiposity

- Has there been a disproportionate increase in central obesity?
- If so, why? What factors are related to location of body fat stores?
- Central obesity related to hormone levels
- Could exposure to endocrine disrupting chemicals play a role due to fetal programming, or by interfering with the action of hormones?

**FIGURE 4** Changes in the prevalence of abdominal obesity as defined by the 90th percentile of WC between NHANES III (1988-1994) and NHANES 1999-2004 according to gender, race/ethnicity, and age

*McCarthy HD et al, British Medical Journal 2003*

*Li, C. et al. Pediatrics 2006;118:e1390-e1398*
Central obesity and hormones

- Estrogen plays a major role in regulation of adipose tissue deposition in both males and females
- Hormone receptors present in adipose tissue (ER, PR, and AR)
- ER’s also present in hypothalamus—primary site in brain that regulates appetite
- Females with central obesity: higher androgens, insulin resistance, lower SHBG
- Hormone replacement therapy results associated with lower BMI and lower central adiposity

Do EDCs affect hormone levels?

- Decreased testosterone with high levels of 2 phthalates (DBP and DEHP) found in study Chinese workers
- Phthalates in breast milk correlated with hormone levels in male infants
- Decreased estrogen and progesterone in females with increases in DDT levels
- Effects on thyroid hormones: PCBs, PDBEs, phthalates and others
Phthalates and Obesity

Phthalate exposure as a possible risk factor—Exposure Sources and Levels

- Exposure to phthalates is widespread
- Supported by data from NHANES
  - 4 phthalates are detected in over 90% of study population
  - Broad range of exposure
  - Interesting patterns with age and sex
- Reason for high levels of exposure is because of multiple uses:
  - Plasticizers in manufacture of consumer products such as plastic toys, medical equipment, food packaging
  - Used in cosmetics, lotions, shampoos, nail polish to hold color and scent
  - Used as solvents in paints, glue, insect repellants, lubricants, and adhesives
  - Does not covalently bind to plastic and may leach into food, beverages or environmental media
- Many potential routes of exposure, although ingestion is thought to be the main route
Phthalate exposure as a possible risk factor—Known or suggested health outcomes

- Very few human studies!
- Lower sperm count and altered motility (Hauser R et al, Epidemiology 2006)
  - Dose response relationships between MBP quartiles and both sperm count and motility
  - Confirmed an earlier smaller study
  - No effects for DEHP metabolites
- Reduced anogenital distance in male infants (Swan S et al; EHP 2005)
  - Exposure to phthalates measured in maternal urine during pregnancy
  - Levels of 4 monoester phthalate metabolites were inversely related to AGD
  - When exposures to phthalates were combined in the analysis, effects were even stronger

Phthalate exposure as a possible risk factor—potential mechanisms of action

- PPARγ agonist
  - Plays a key role in lipid and glucose metabolism
- Ovarian toxin
  - Decreased estradiol secretion and caused prolonged estrous cycles and anovulation in female rats
  - May disturb the estrogen/androgen balance
  - Androgen/estrogen balance may be associated with central adiposity
Geometric means, selected EDCs, by overweight status in young girls (Wolff et al, 2007)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>BMI &lt; 85%</th>
<th>BMI &gt;85%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterolactone</td>
<td>513.0</td>
<td>174.0*</td>
</tr>
<tr>
<td>MECPP</td>
<td>86.6</td>
<td>93.4</td>
</tr>
<tr>
<td>MEHHP</td>
<td>43.0</td>
<td>56.1</td>
</tr>
<tr>
<td>MEOHP</td>
<td>28.8</td>
<td>35.8</td>
</tr>
<tr>
<td>MEHP</td>
<td>5.5</td>
<td>6.5</td>
</tr>
<tr>
<td>MEP</td>
<td>102.0</td>
<td>144.0</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>3.7</td>
<td>2.2*</td>
</tr>
</tbody>
</table>

*difference significant at p<0.05

Other clues for role of EDCs in obesity

- Diabetes associated with POP’s?
  - 2 suggestive studies
- Diethylstilbestrol (DES)
  - In utero exposure to DES resulted in fatter offspring (R. Newbold et al)
  - DES used extensively in agriculture to fatten cows and chickens
  - DES may affect adult hormone levels (higher androgens)
  - DES and third generation effects
- Several drugs (especially psychiatric) related to weight gain and central adiposity
  - Could exposure to low levels of multiple environmental chemicals have similar effects?
  - If so, what are the mechanisms of action?
Challenges in studying possible role of EDC’s and obesity

- How do we prioritize chemicals to study?
  - Which ones have biologic plausibility for association with obesity
- Measurement issues, especially for chemicals which are not persistent
- Time period of exposure—effects may be important in one life stage but not in others
  - Life course epidemiologic approach necessary

Limitations of current epidemiologic studies

- Mostly cross-sectional to date
- BMI: proxy measure that misclassifies some individuals
  - Is central adiposity (waist circumference or waist to hip ratio) a better measure?
- Analytic challenges
  - Critical time periods for exposure?
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Approaches to study environmental chemical exposure and obesity in epidemiologic studies

- Existing cross-sectional data
  - NHANES
- Special exposure cohorts
  - DES, Agent Orange, PCB exposure cohorts, Seveso, others?
- On-going cohort studies (especially pregnancy cohorts) with stored biological specimens
  - Incorporate hypotheses for specific environmental chemicals
- Initiate new cohort studies
- Interdisciplinary collaboration