Obesity, Sex and the Pathophysiology of MS

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Disclosures

- Site Principal Investigator for 2 industry-sponsored phase 3 clinical trials -Biogen Idec and Hoffman LaRoche, and one industry-sponsored diagnostic assay observational study - Biogen-Idec.
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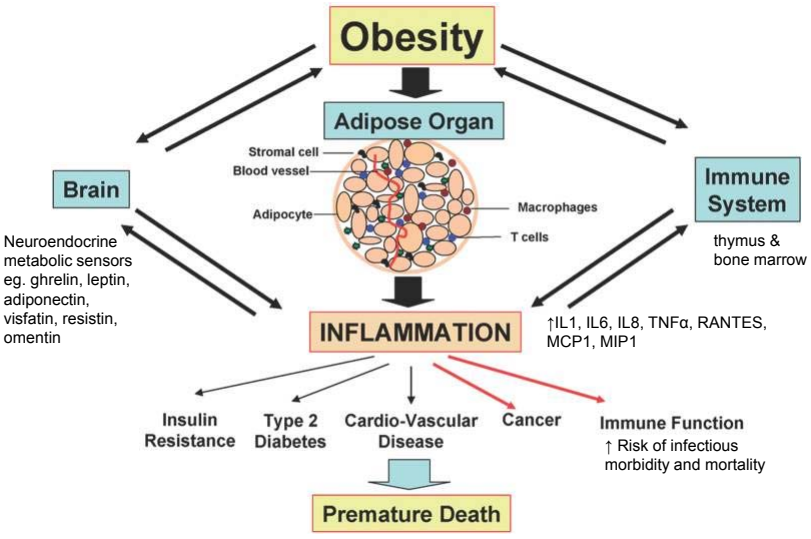
Overview

- Prevalence of obesity has tripled over the past 30 years
- Obesity is a low grade inflammatory state
- Evidence linking obesity to pediatric and adult-onset MS
- Potential mechanisms whereby obesity could increase the risk of MS
- Obesity is becoming the single most important MS risk factor (highest attributable risk)

Obesity: chronic low grade inflammation

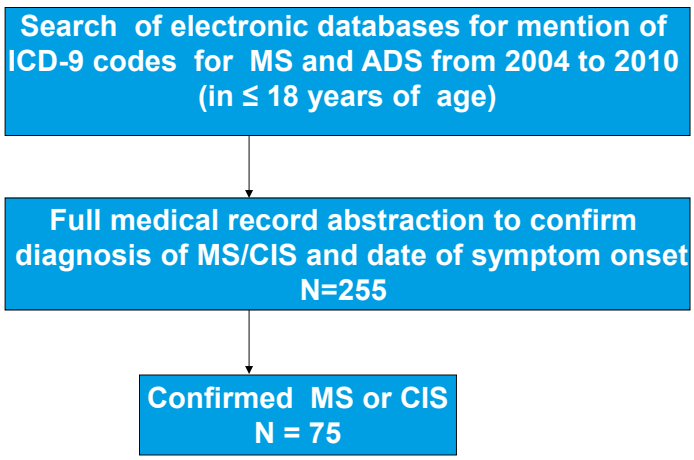


VD Dixit, J Leukoc Biol 2008

Childhood Obesity and Pediatric MS

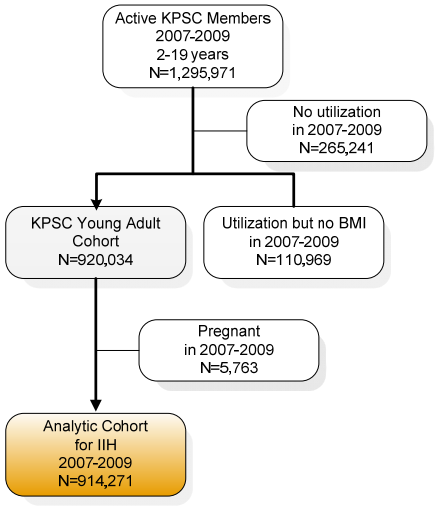
- Pediatric onset MS and clinically isolated syndrome is increasingly recognized
- Over 30% of kids in the US are overweight or obese
- Objective: to determine whether childhood obesity is a risk factor for developing pediatric MS and Clinically isolated syndrome (CIS)
- Method: Cross-linked data from KPSC Pediatric Acquired Demyelinating Disease (ADS) Cohort with the KPSC Children's Health Study

KPSC Pediatric Acquired CNS Demyelinating Diseases Cohort



CIS -CNS demyelinating event without encephalopathy .
MS- 2 or more episodes, or single episode with new gad or T2 lesion at 3 months after initial event.
ADEM not included.
TM were included only after exclusion of infectious, vascular other inflammatory causes.

KPSC Children's Health Study

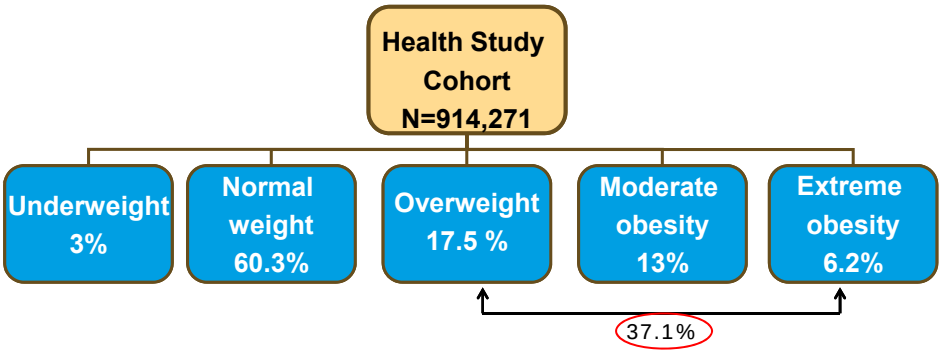


Weight classes for children

- Weight classes assigned based on sex specific BMI- for –age growth charts developed by CDC and WHO definition.
- For cases most recent body weight and height prior to symptom onset.

Underweight:	<5th percentile		
Normal weight:	5th - 84.9th percentile	and	BMI <25
Overweight:	>=85th percentile	or	BMI >=25
Moderate Obesity:	>=95th percentile	or	BMI >=30
Extreme Obesity:	>=1.2 x 95th percentile	or	BMI >=35

Health Study Demographics



Children who were extremely obese were more likely to be

- males (57% vs 49%, p<0.001)
- Hispanic (62% vs 47%, p<0.001) and
- adolescents/teenagers (50% vs 39% p<0.001) than those of normal weight

Table 1: Demographic characteristics of youth with and without multiple sclerosis or clinically isolated syndrome

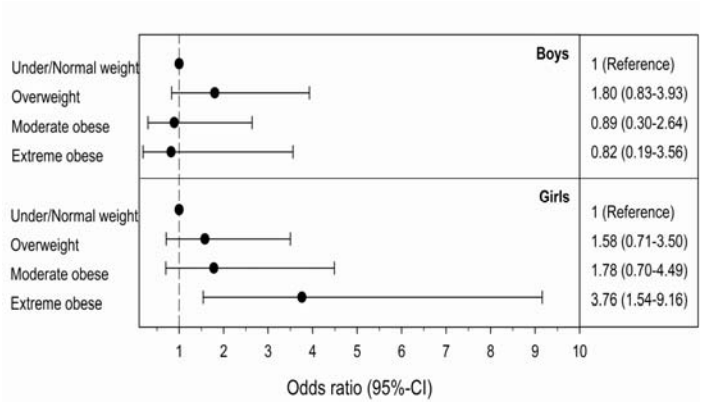
	Youth with MS/CIS (n=75)		Youth without MS/CIS (n=913,097)		
	n	%	n	%	P-value
Sex					0.4
Male	34	45.3	459,116	50.3	
Female	41	54.7	453,981	49.7	
Age					<0.001
2-11	21	28.0	448,559	49.1	
12-18	54	72.0	467.54	50	
Race/Ethnicity					0.003
Non-Hispanic White	17	22.7	193,262	21.2	
Hispanic	39	52.0	464,701	50.9	
Black	12	16.0	68,359	7.5	
Asian or Pacific Islander	7	9.3	62,399	6.8	
Other/Unknown	0	0.0	124,376	13.6	
Weight class					0.03
Under/normal weight	37	49.3	579,087	63.4	
Overweight	19	25.3	159,043	17.4	
Moderately obese	10	13.3	118,776	13	
Extremely obese	9	12.0	56,191	6.2	
Neighborhood education					0.8
Less than high school	22	29.1	273,929	28.5	
High school graduate	16	22.2	199,968	21.6	
Some college	23	29.8	270,285	30.3	
Bachelor degree or higher	14	18.9	168,914	19.6	

Association between Pediatric MS/CIS and increasing weight class according to age group

		All MS/CIS		2-11 years at onset		12-18 years at onset	
	Total n	Cases N=75	Adjusted OR(95%-CI)[1]	Cases N=21	Adjusted OR(95%-CI)[1]	Cases N=54	Adjusted OR(95%-CI)[1]
Weight class		p trend = 0.05		p trend = 0.92		p trend = 0.03	
Under/normal weight	579,124	37	1.00 (Reference)	12	1.00 (Reference)	25	1.00 (Reference)
Overweight	159,062	17	1.68 (0.96-2.93)	5	1.46 (0.51-4.17)	14	1.71 (0.89-3.31)
Moderately obese	118,786	10	1.28 (0.63-2.58)	3	0.99 (0.28-3.56)	7	1.29 (0.55-3.01)
Extremely obese	56,200	9	2.10 (1.00-4.41)	1	0.72 (0.09-5.65)	8	2.57 (1.15-5.78)
Female sex	454,022	41	1.21 (0.77-1.92)	8	0.65 (0.27-1.56)	33	1.60 (0.92-2.77)

[1]All odds ratios (OR) are mutually adjusted for age, sex, neighborhood education

Association between weight class and pediatric MS/CIS by sex



OR adjusted age at onset and race/ethnicity

P value for girls 0.005, boys 0.93

Clinical characteristics of MS/CIS cases according to weight class

	Normal weight n=37	Overweight n=19	Moderately obese n=10	Extremely obese n=9	Total n=75	P value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Female sex	19 (51.4)	9 (47.4)	6 (60.0)	7 (77.8)	41 (54.7)	0.16
Clinical Symptoms at presentation						
Optic neuritis	18 (48.6)	7 (36.8)	5 (50.0)	1 (11.1)	31 (41.3)	0.33
Transverse myelitis	7 (18.9)	1 (5.3)	4 (40.0)	5 (55.6)	17 (22.7)	0.003
Other forms of CIS	12 (32.4)	11(57.9)	1 (10.0)	3 (33.3)	27 (36.0)	0.15
Multiple Sclerosis	15 (40.5)	9 (47.3)	5 (50.0)	6 (66.7)	35 (46.7)	0.26

Summary of Findings

- Interaction between childhood obesity and sex
- increased risk of pediatric onset MS/CIS in girls but not in boys
- Female sex and black race is associated with increased risk of MS/CIS
- Obesity may influence prognosis/clinical subtype as well

Limitations and Strengths

Limitation

- Small sample size of young children with MS/CIS (rare in prepubertal age group)
- Age cut off instead of tanner stages to estimate puberty
- Lack of follow up into adulthood

Strengths

- First population-based study to examine this relationship
- Large base population with moderate and extremely obese children
- Accuracy of body size data

Childhood Obesity and Adult-onset MS

study	design	asembly yrs	MS cases N	obesity	obese BMI≥30 N cs/cntrl	results
Munger et al 2009	NHS, cohort of US nurses	1976-2003	593	Self report ages 5, 10, 18, 20	27/3857	**age 18 ♀ 2.25 (1.5-3.4)** no effect age 5 or 10
Hedeström et al 2012	Incident MS/ volunteer cntrl 2:1 Sweden	2005-2011	1571	Self report age 20	72/81 BMI ≥27	♀ **2.2 (1.5-3.2)**
						♂ **2.1 (1.0-4.3)**
Munger et al 2013	Cohort, Copenhagen schools	1930-1983 7-13 yrs	774 (1968-2004)	School records Ages 7-13	51-60/?	♀ **1.6 -1.95 (1.2-2.7)**
						♂ **1.3 -1.8 (0.8 -2.9)**
Hedeström et al 2013 HLA+obese worse than either	Sweden; KPNC prevalent MS case -control study	2005-2012;	1510; 937 MS (609 controls)	Self report age 20	80/24; KPNC 60/9 BMI ≥27	HLA-DR15- **1.9 (1.3-2.7)**
						HLA-DR15+ **7.9 (4.9-12.7)**

Swedish increased risk with BMI ≥27 and if HLA-DR15+ then risk even higher
Danish study showed obesity at any age 7-13 increased risk of MS in adulthood

Adult Obesity and Adult-onset MS/CIS

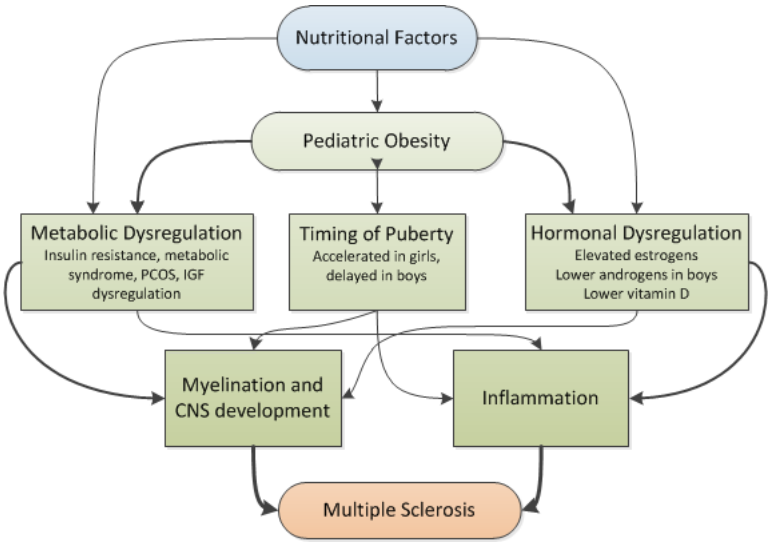
study	design	asembly yrs	MS cases/ control	obesity	obese BMI≥30 N cs/cntrl	results
Munger et al 2009	NHS, cohort of US nurses	1976-2003	593	Self report study entry (ages 25-55)	59/3857	♀ 0.91 (0.46-1.79) BMI≥30
Ponsonby et al 2013	Ausimmune Study, first demyelinating event	2003-2006	282/558	Obtained at study visit	?	0.99 (0.95-1.02) BMI continuous
						5.5 (0.36-83.3) ≤25yrs, BMI≥30

Has not been carefully examined; no conclusions can be drawn

Summary

- Possible interaction of adolescent obesity and sex
  - accelerates symptom onset in girls but not boys
- Likely underestimates of risk in extremely obese individuals
- Unclear if critical risk period adolescence or early childhood obesity as well

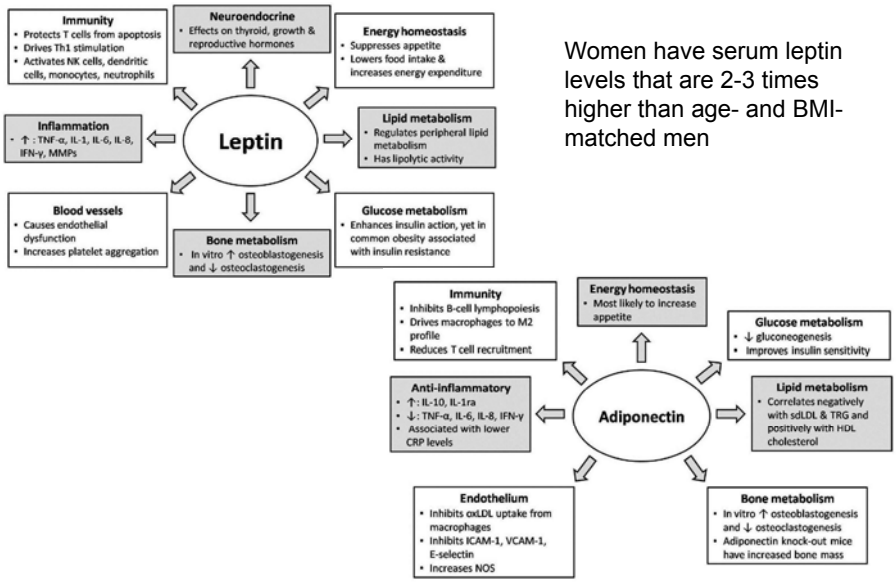
Possible Biological Mechanisms



Caloric Restriction, Major Adipokines

Factor	Clinical findings	Animal/cell studies
Obesity & Caloric Restriction	• Adolescent obesity & MS risk • MS and comorbidities including obesity associated with more disability (Marrie Lancet Neuro 2010)	• CR prior to induction reduces severity of EAE • Caloric excess has no effect on EAE (Piccio etal J Leukoc Biol 2008)
Leptin (increased by excess caloric intake)	• Expressed in MS lesions (Lock et al Nat Med 2002) • Elevated CSF and serum levels correlated with low Treg cells (Matarese et al PNAS 2005)	• KO mice do not develop EAE (Matarese G et al J Immunol 2001) • KO mice impaired global brain development including myelination (Udagawa et al Endocrinology 2006) • Neutralization decreases severity of EAE (DeRosa et al J Clin Invest 2006)
Adiponectin (decreased by excess caloric intake)	• Decreased serum levels in MS (Musabak etal Neuroimmunomodulation 2011; Kraszula et al Neurol Neurochir Pol 2012) • Increased CSF levels (Hietaharju et al Eur J Neurol 2010)	• KO mice increases disease severity in EAE reversed by exogenous administration (Piccio et al Eur J Immunol 2013)

Complex Actions of Leptin and Adiponectin



Women have serum leptin levels that are 2-3 times higher than age- and BMI-matched men

Derdemezis et al Clin Exp Rheumatol 2011; 29: 712-27

Obesity and Gut Microbiota

- Clear 2-way relationship in animal models
  - High fat, high carb diet changes gut microbiota
  - Obese mice (whether genetically manipulated or through diet) microbiota highly efficient transfer calories from diet to host and improving fat storage efficiency
- Evidence in humans is not so clear (except breastfed infants)
  - Complex relationship between food content of prebiotics, probiotics, and calories and antibiotic exposure
  - The effect of gut microbiota is dependent upon
    - Host factors (age, ecological diet/baseline nutrition)
    - Probiotic strain (weight gain or loss)

Conclusions

- Obesity epidemic will likely lead to increased incidence MS/CIS particularly in adolescent girls and women and to a lesser extent, men
- Childhood obesity is becoming ***the most important risk factor for MS*** (highest attributable risk) in women and likely to parallel cigarette smoking in men
- Multiple biological mediators are likely at play
- Studies of weight trajectories stratified by sex are needed to
  - understand the critical risk period and
  - critical period for weight loss interventions

Conclusions

- Role of obesity and weight loss on MS prognosis biologically plausible and should be studied further
- Helping obese individuals loose weight is a complex behavioral change that requires extensive team work in the health care setting and engagement of community partners including city planners, schools and policy makers
- Use the opportunity at clinic visits to encourage patients to loose weight and utilize community resources to do this successfully

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