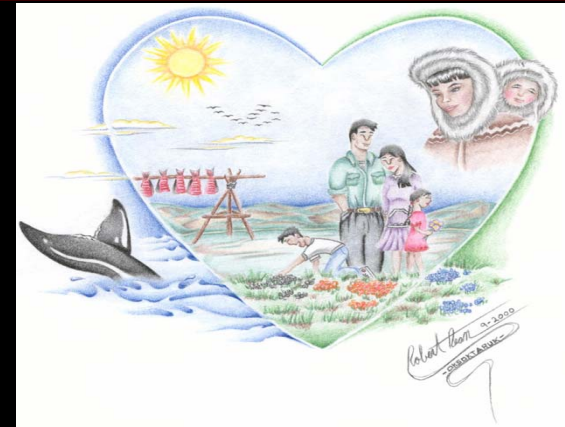


Risk Factors for Preclinical Atherosclerosis



Barbara V Howard, PhD for the
GOCADAN investigators

Background

- Although early reports suggested that CVD was uncommon in Eskimos, state mortality data and hospital records suggest that CVD is now common and may be increasing
- Traditional Eskimo lifestyle relied on subsistence hunting and fishing and thus a diet high in omega-3 fatty acids. Intake is changing with changing lifestyles.
- It is not clear which CVD risk factors and how changes in lifestyle are related to CVD in Eskimos

Objectives

- **To evaluate the prevalence of pre-clinical atherosclerosis using carotid ultrasound**
- **To assess relationships with traditional CVD risk factors**
- **To evaluate relationships with fatty acid consumption**

Population

Village	Eligible	Recruited	
	#	#	%
Brevig Mission	123	112	91
Elim	141	132	94
Golovin	58	48	83
Koyuk	131	115	87
Shaktoolik	107	83	78
Teller	117	24	21
Unalakleet	350	255	73
White Mt.	97	75	77
Nome	829	370	45

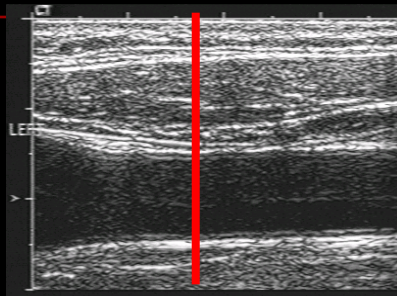
Community Involvement

- Study design and implementation
- Eskimo investigators and staff
- Medical care to participants
- Data used for community health initiatives
- Education of community youth
- Participation in community health initiatives

Baseline Characteristics

Variable	Men (537)	Women (677)	p value
Age (yrs)	42 (16)	43 (16)	.384
BMI (kg/m ²)	26.6 (5.1)	28.6 (6.3)	<.001
Hypertension	23%	20%	.053
Diabetes	2.1%	4.9%	.005
Current Smoker	63%	57%	.119
LDL chol (mg/dl)	117	115	.240
HDL chol (mg/dl)	53	63	.010
CRP (mg/L)	3.1 (7.1)	3.5 (13.7)	.431

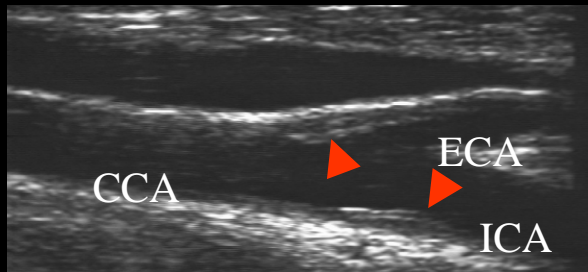
Assessment of Carotid Atherosclerosis



Near Wall

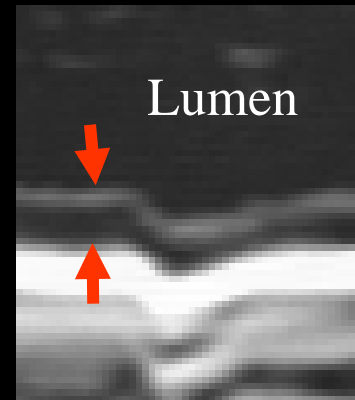
Far Wall

2-D Guided M-Mode of the
Distal Common Carotid Artery



Plaque - Focal Protrusion $>50\%$
Thickness of Surrounding Wall

IMT

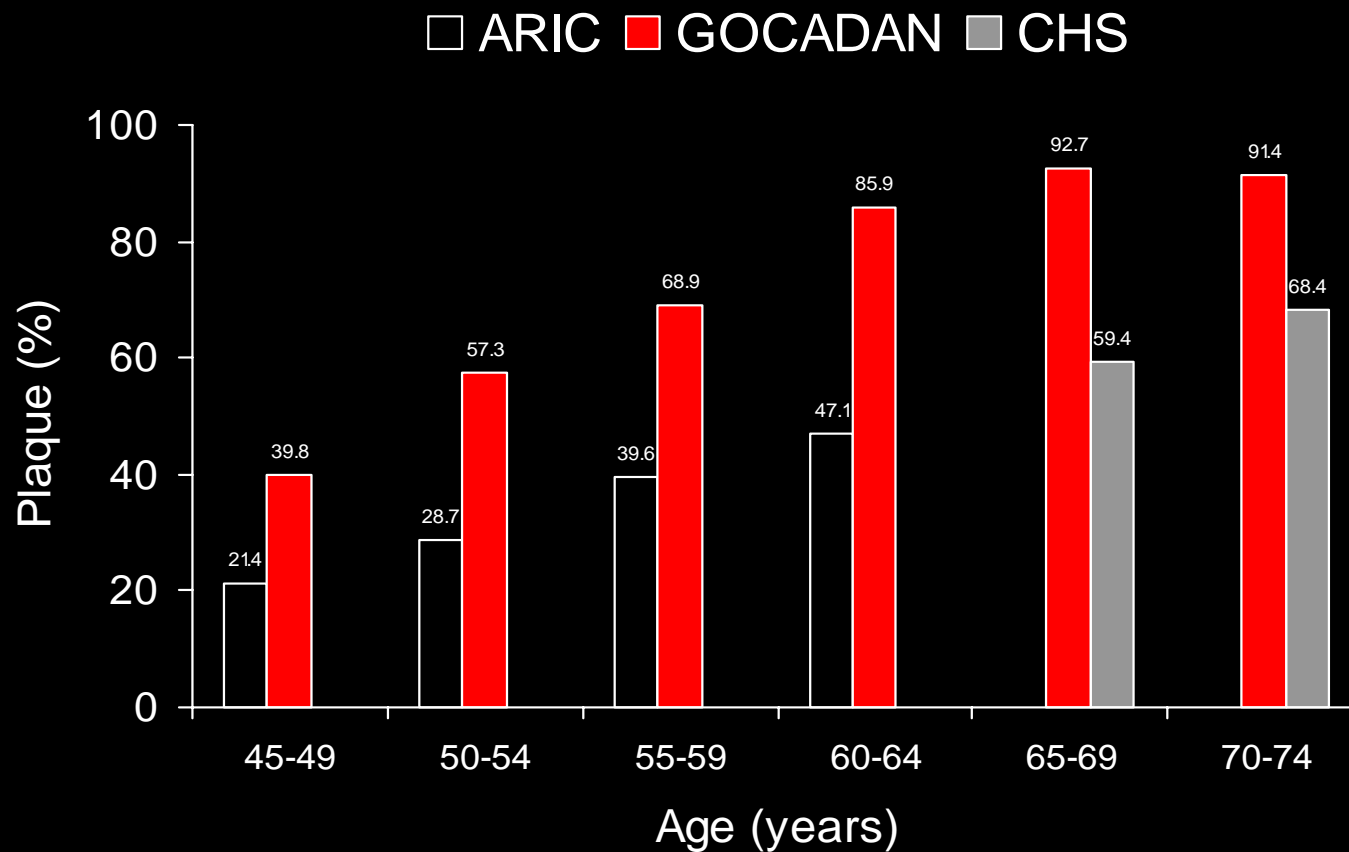


← Intima

← Media

← Adventitia

Prevalence of Plaque Compared to US Populations



Multivariate Correlates: Carotid IMT

Variable	Beta	B (95% CI)	P value
Age (per 10 years)	0.665	0.061 (0.056-0.066)	<0.001
Body mass index	0.055	0.001 (0.000-0.003)	0.024
Sex (male=0, female=1)	-0.101	-0.029(-0.043--0.016)	<0.001
Hypertension	0.062	0.022 (0.004-0.039)	0.016
LDL cholesterol (mg/dl)	0.010	0.000 (0.000-0.000)	0.680
HDL cholesterol (mg/dl)	-0.049	0.000 (-0.001-0.000)	0.044
Smoke (current vs. others)	0.019	0.006 (-0.011-0.022)	0.507
DM (DM vs. others)	0.064	0.064 (0.014-0.088)	0.006

Logistic Regression Analysis: Carotid Plaque

Variable	Beta	Odds ratio (95% CI)	P value
Age (per 10 years)	1.63	5.09 (4.05-6.39)	<0.001
Body mass index	-0.08	0.92 (0.88-0.96)	<0.001
Sex (male=0, female=1)	0.22	1.25 (0.83-1.88)	0.289
Hypertension	0.55	1.74 (1.07-2.82)	0.025
LDL (mg/dl)	0.006	1.006 (1.00-1.01)	0.035
HDL (mg/dl)	0.001	1.001 (0.99-1.01)	0.913
Smoke (current vs. others)	0.80	2.23 (1.23-4.04)	0.008
DM (DM vs. others)	0.654	1.92 (0.54-6.83)	0.312

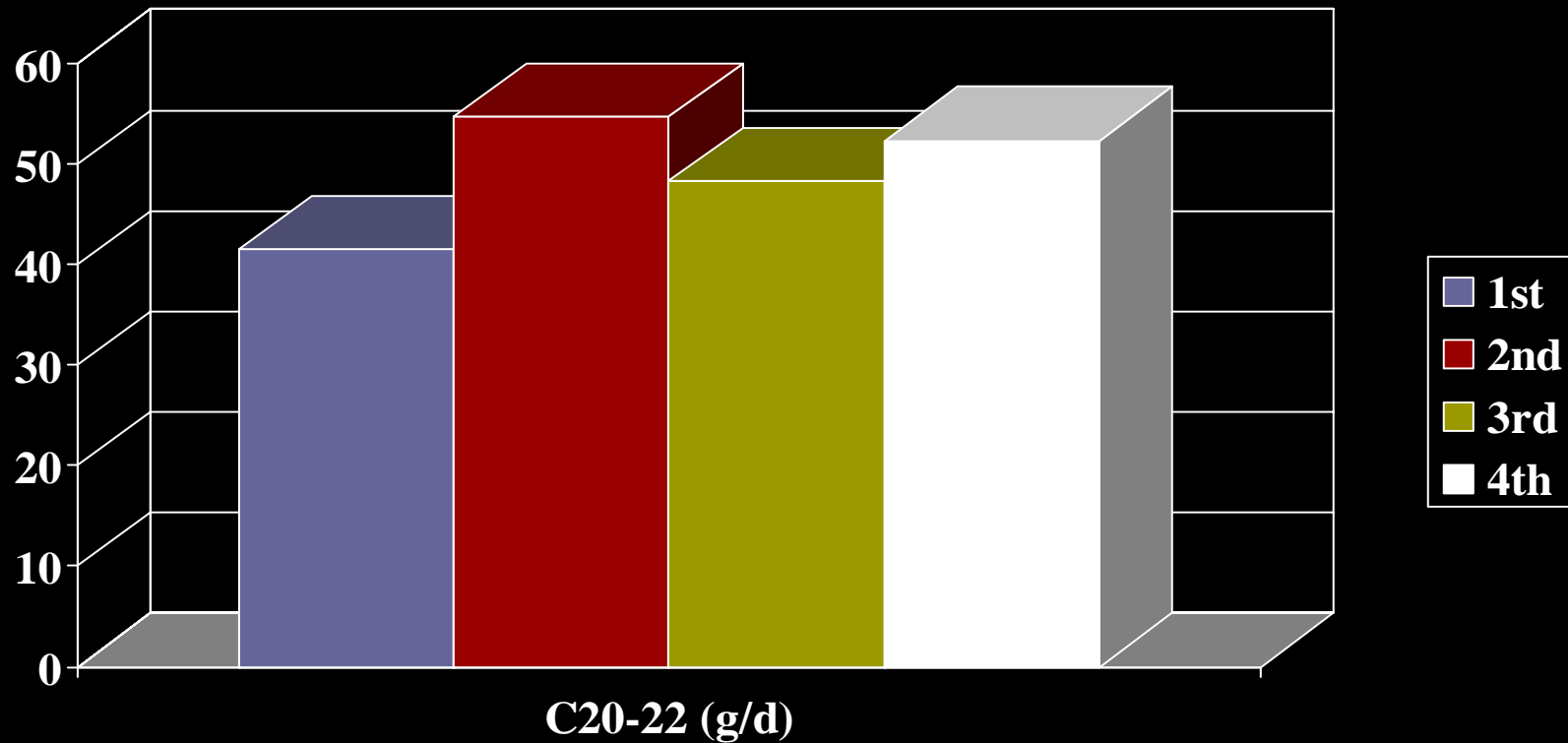
Multivariate Correlates: Plaque Score

Variable	Beta	B(95% CI)	P value
Age (per 10 years)	0.657	0.241 (0.221-0.262)	<0.001
Body mass index	-0.147	-0.015 (-0.020--0.010)	<0.001
Sex (male=0, female=1)	-0.047	-0.055 (-0.109-0.002)	0.043
Hypertension	0.070	0.097 (0.026-0.168)	0.007
LDL (mg/dl)	-0.007	0.000 (-0.001- 0.001)	0.760
HDL (mg/dl)	-0.029	-0.001 (-0.002-0.001)	0.227
Smoke (current vs. others)	0.040	0.047 (-0.020-0.114)	0.166
DM (DM vs. others)	0.049	0.156 (0.009-0.303)	0.037
C-reactive protein (mg/dl)	0.075	0.034 (0.013-0.054)	0.001

Dietary Intake

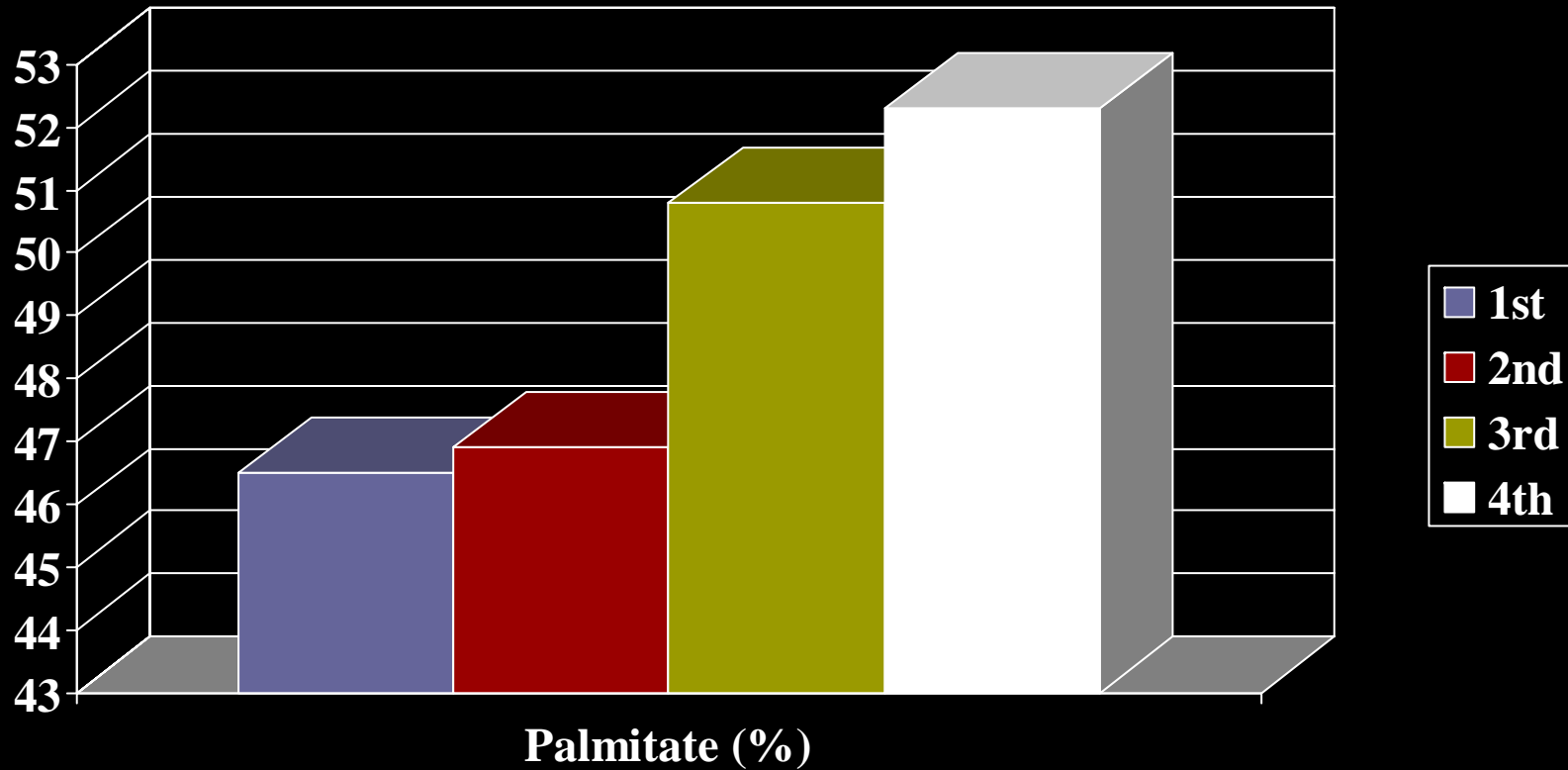
Nutrient	Mean	Inter-quartile Range
Carbohydrate (%)	47.2	40.2-53.5
Protein (%)	15.0	12.3-17.4
Fat (%)	38.8	32.8-44.0
Saturated fat (%)	13.1	10.7-15.3
Omega-3 (g/day)	4.9	2.2-6.1
C20-22 (g/day)	2.9	0.9-3.5

C20-22 Quartile and Prevalence of Plaque



$p = .73$ (age, gender); $p = .92$ (fully adjusted)

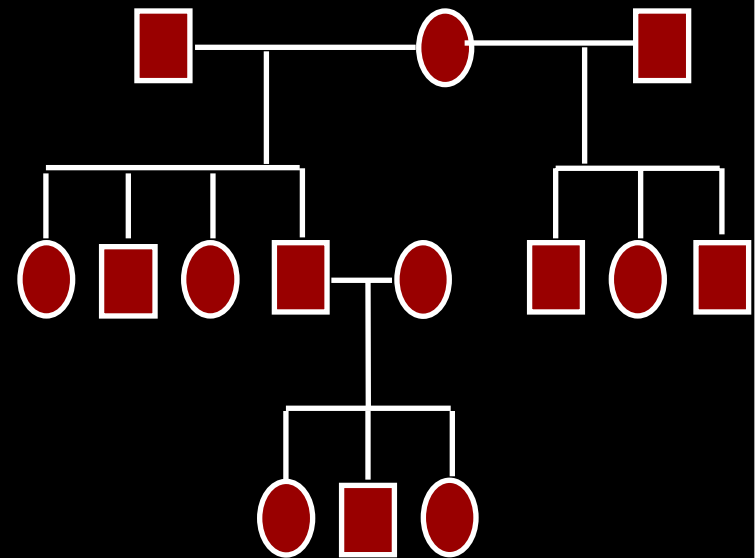
Palmitate Quartile and Prevalence of Plaque



$p = .04$ (age, gender); $p = .02$ (fully adjusted)

Genetic Analyses in GOCADAN

- Advantage of large extended families
- Availability of data on risk factors and preclinical disease
- Availability data on environmental exposures



Heritabilities for CVD Related Phenotypes

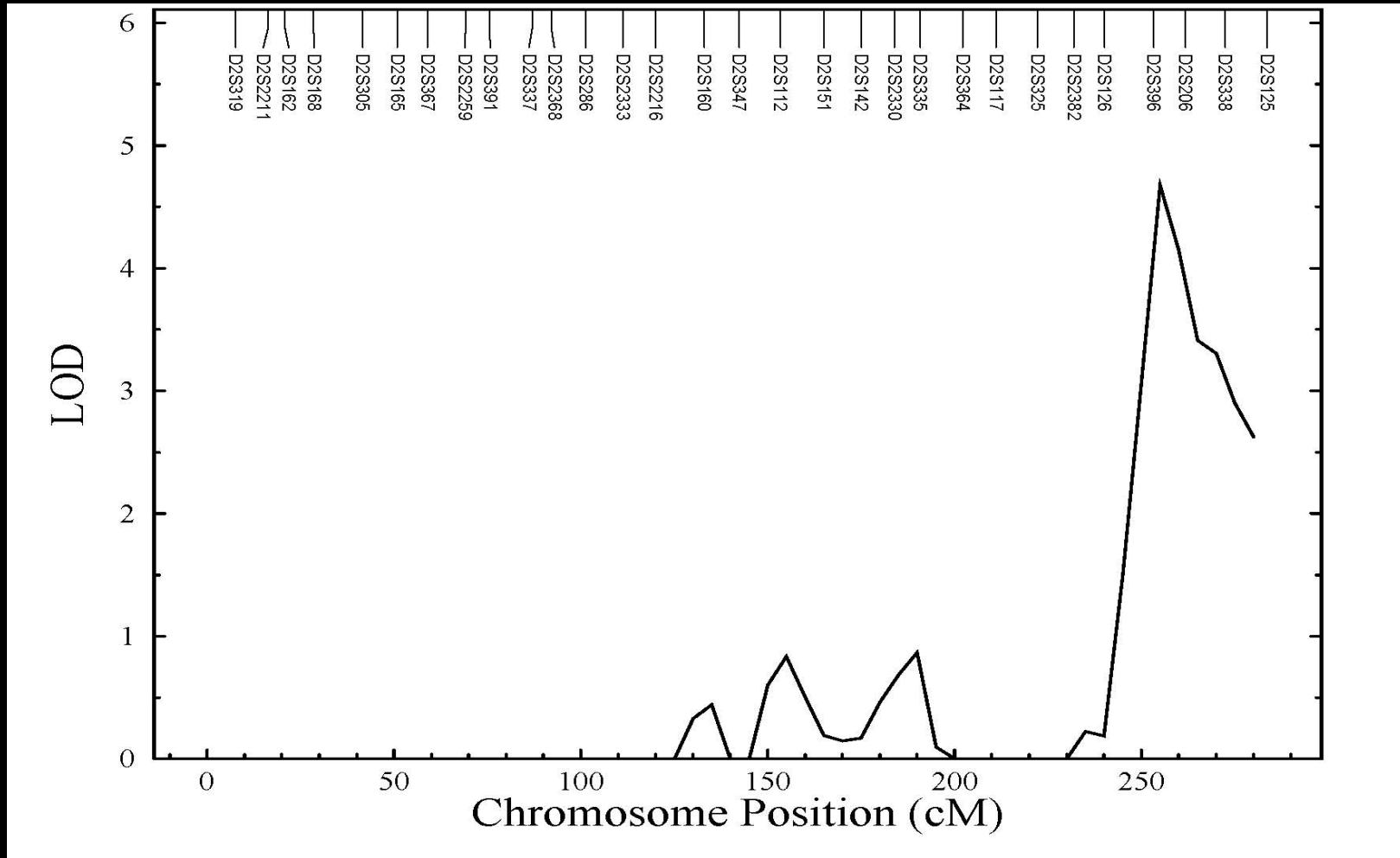
Trait	h ²	Trait	h ²
SSP	0.49	Dia BP	0.30
Tricep	0.45	ApoA1	0.40
BMI	0.56	ApoB	0.32
FM	0.55	Lp(a)	0.95
W/H Ratio	0.35	HDL-C	0.45
Waist	0.49	LDL-C	0.25
Wt	0.58	TG	0.24
% body fat	0.44	LDL size	0.34
Left DD	0.39	HDL size	0.33
Left SD	0.29	FGI	0.24
Right DD	0.39	HbA1c	0.50
Right SD	0.38	Fibrin	0.43
Right IMT	0.16	Ferritin	0.22
Sys BP	0.43	Hb	0.33

*534 female, 420 male
all h² were significant at p ≤ 0.001

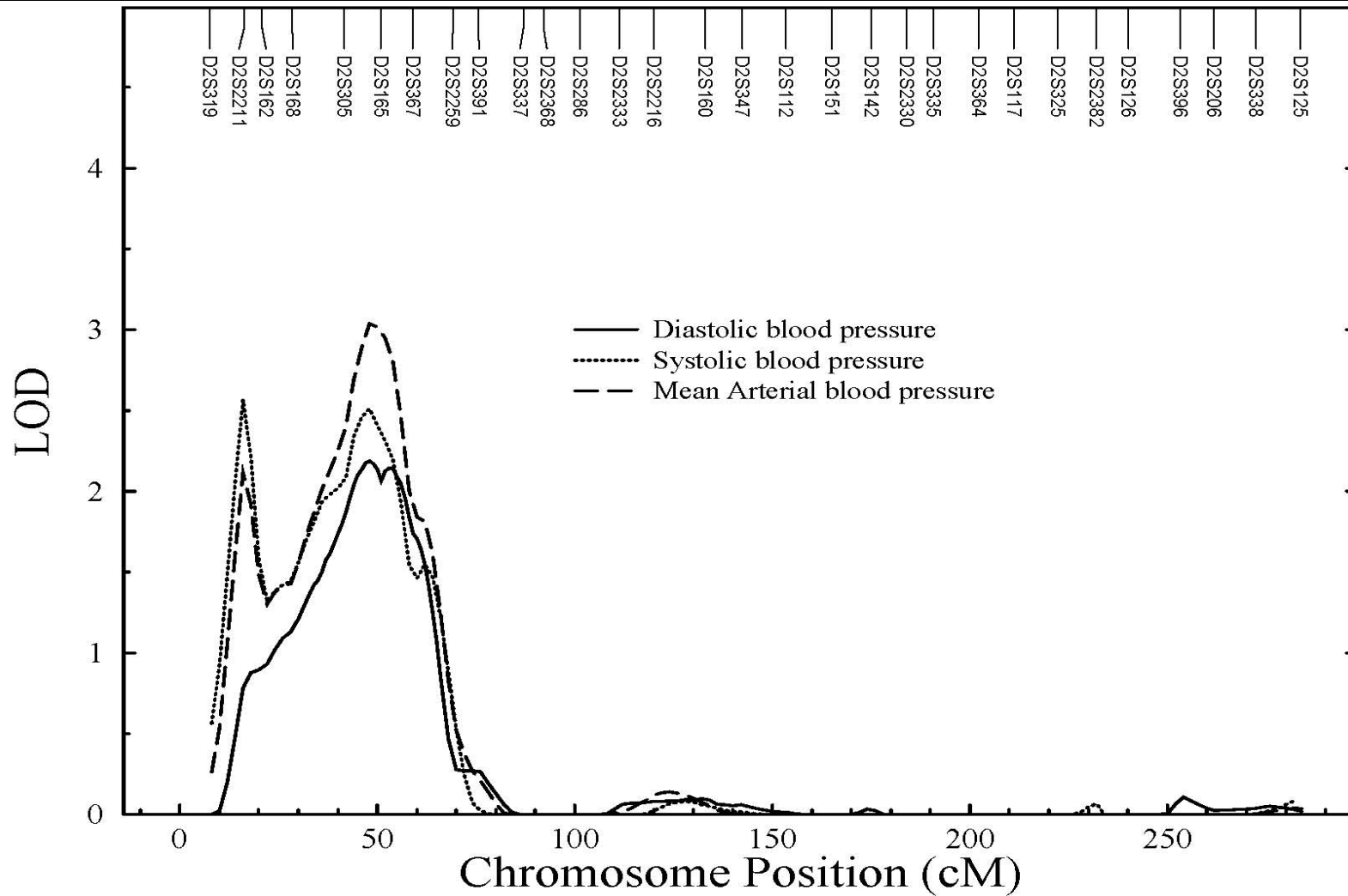
Linkage Signals from Preliminary Genome Scan

TRAIT	CHROM	LOD	NEAREST	LOC (Mb)	POS CANDIDATE	Mb AWAY
DM	2q	4.7	<i>D2S396</i>	230.5	<i>IRS1</i>	3.1
HDL	19p13	3.9	<i>D19S221</i>	12.4	<i>LDLR</i>	1.4
MAP	2p23	3.0	<i>D2S165</i>	28.5	<i>KCNK3</i>	< 3
ApoB	17q21	3.0	<i>D17S928</i>	77.8		
Fer	17q25	3.0	<i>D17S785</i>	72		
SPB	5q35	2.6	<i>D5S400</i>	168.3	<i>DRD1</i>	< 6
HDL	17p13	2.5	<i>D17S938</i>	6.2	<i>GLUT4, SHBG</i>	< 1 < 2
SST	15q26	2.2	<i>D15S205</i>	82	<i>PLIN</i>	< 6
LDL	14	2.0	<i>D14S280 - D14S65</i>	91.2 - 96.6	<i>TNFAIP2 TSHR</i>	< 8 < 10
TC	18	2.0	<i>D18S464 - D18S53</i>	9.9 - 11.5	<i>MC2R MC5R</i>	< 5 < 5
LDL	19	2.0	<i>D19S902</i>	53	<i>ApoE</i>	< 2
ApoA1	11	1.9	<i>D11S4151 - D11S1320</i>	125.7 - 131.4	<i>ApoA1</i>	< 15

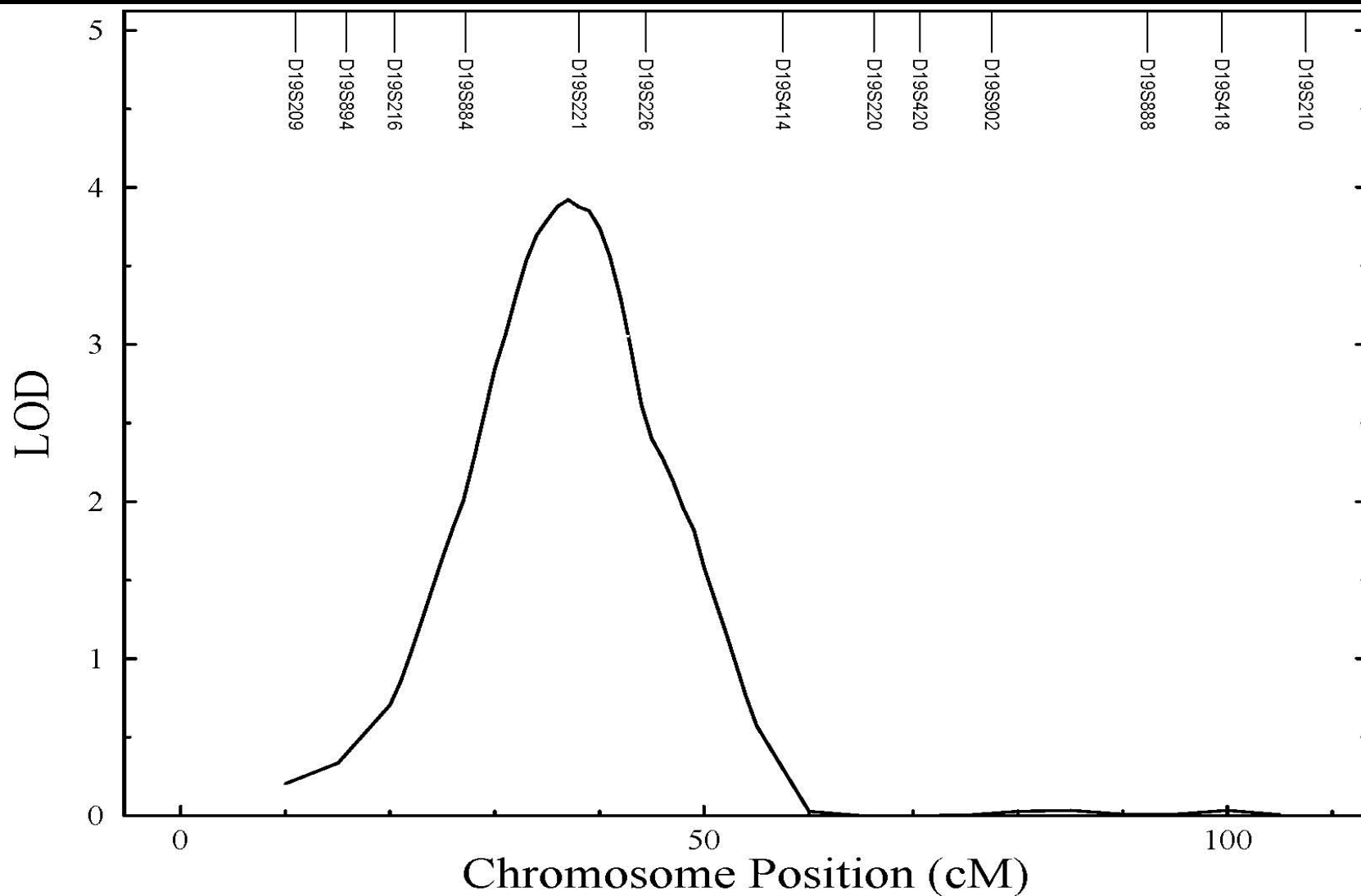
Chromosome 2 : Diabetes/IGT vs. Normal Glucose



Chromosome 2 : Blood Pressure Measures



Chromosome 19 : HDL Levels



Clusters of GOCADAN Linkage Signals

TRAIT	CHRM	LOD	Nearest Marker	LOC (Mb)
HDL	19p13	3.9	<i>D19S221</i>	12.4
LSize	"	2.5	"	"
HSize	"	2.3	"	"
AvArtPrs	2	3.0	<i>D2S165</i>	28.5
AvDias	2	2.6	<i>D2S2211</i>	7.4
AvSys	2	2.4	<i>D2S305</i>	19.3
AvSubs	15q26	2.2	<i>D15S205</i>	82
Fatmass	15q26	2.0	"	"
PerFat	15q26	1.9	"	"
LDL	19	2.0	<i>D19S902</i>	53
TC	19	2.0	"	"
Weight	19	2.0	"	"
FFM	19	1.9	"	"

CONCLUSIONS

- Preclinical atherosclerosis is more prevalent in Alaska Eskimos than in other US populations
- The presence and extent of carotid atherosclerosis and IMT are strongly related to traditional CVD risk factors, similar to other populations.
- Atherosclerosis is not related to intake of omega-3 fatty acids, but is related to intake of saturated fatty acids

CONCLUSIONS

- The high prevalence of atherosclerosis may be related to high rates of smoking or as yet unidentified genetic or environmental factors.
- Cardio-protective effects of omega-3 fatty acids may not include retardation of atherosclerosis

CONCLUSIONS

- There are promising linkage signals for several risk factors and for measures of subclinical CVD
- Clustering of linkage signals provides evidence for joint genetic control of related risk factors
- Fine mapping and RNA expression analysis will further explore these initial findings
- This information should lead to new approaches for prevention and treatment strategies

The investigators are grateful
to the members and leadership
of the communities
for their advice and guidance

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