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Lipid Guidelines in Cardiovascular Risk Stratification

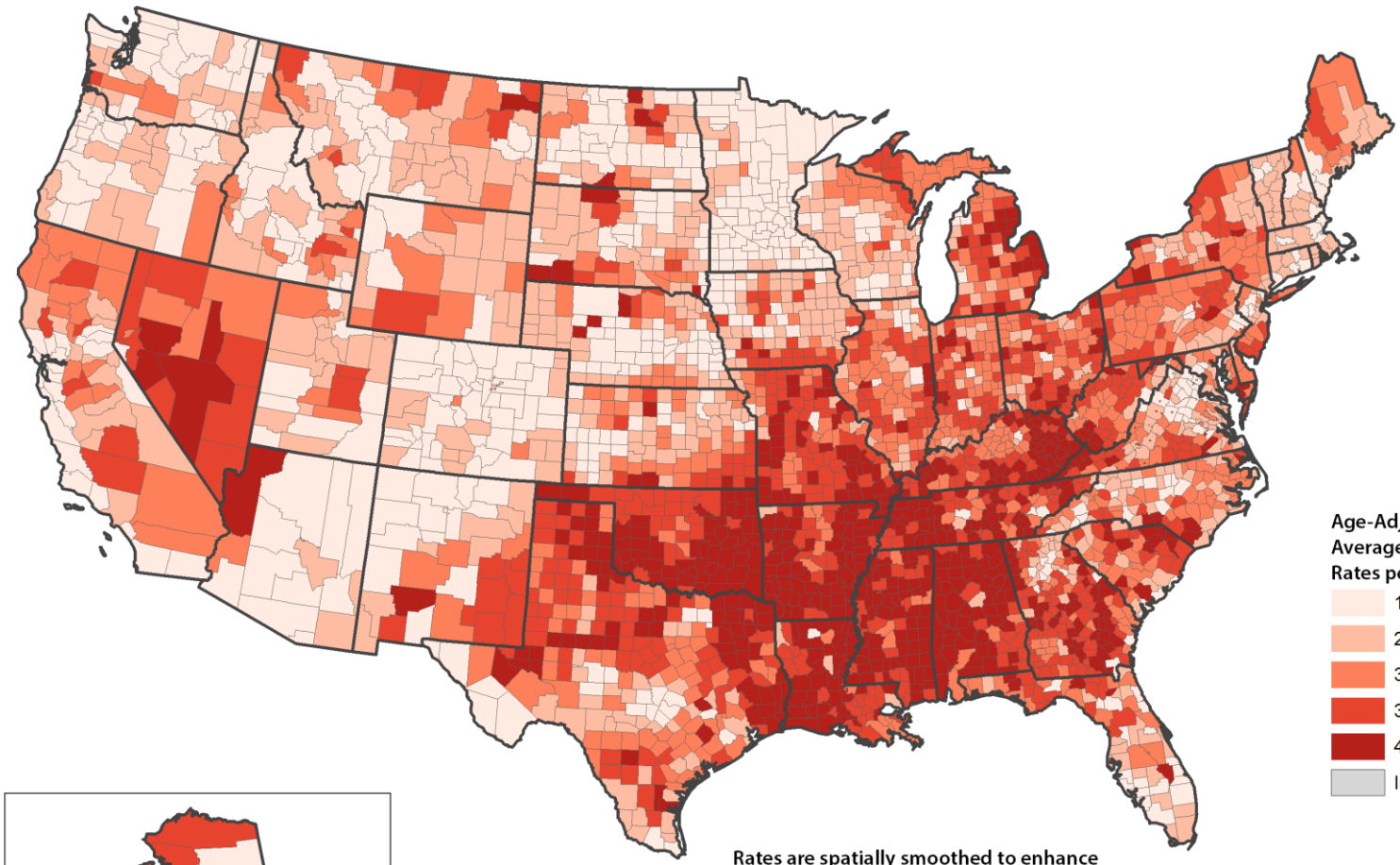
Fasting vs Non-Fasting Lipid Profiles?

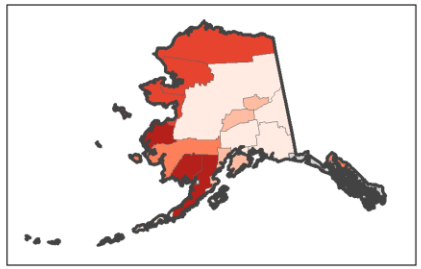
Khosrow Adeli PhD, FCACB, DABCC
Senior Scientist, Molecular Medicine,
Research Institute, The Hospital for Sick Children
University of Toronto
Toronto, Canada

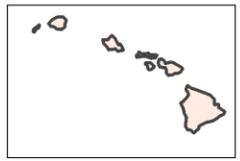
Global Burden of Cardiovascular Disease – *Key Facts*

- CVDs are the number 1 cause of death globally: more people die annually from CVDs than from any other cause.
- An estimated 17.7 million people died from CVDs in 2015, representing 31% of all global deaths. Over three quarters of CVD deaths take place in low- and middle-income countries.
- *Most cardiovascular diseases can be prevented* by addressing behavioural risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies.
- People with cardiovascular disease or who are at high cardiovascular risk (due to the presence of one or more risk factors such as hypertension, diabetes, hyperlipidaemia or already established disease) need early detection and management using counselling and medicines, as appropriate.

Heart Disease Death Rates, 2014-2016
Adults, Ages 35 +, by County







Age-Adjusted
Average Annual
Rates per 100,000

- 103.4 - 284.2
- 284.3 - 324.9
- 325.0 - 365.9
- 366.0 - 426.5
- 426.6 - 1170.5
- Insufficient Data

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics

www.cdc.gov/dhdsp/maps

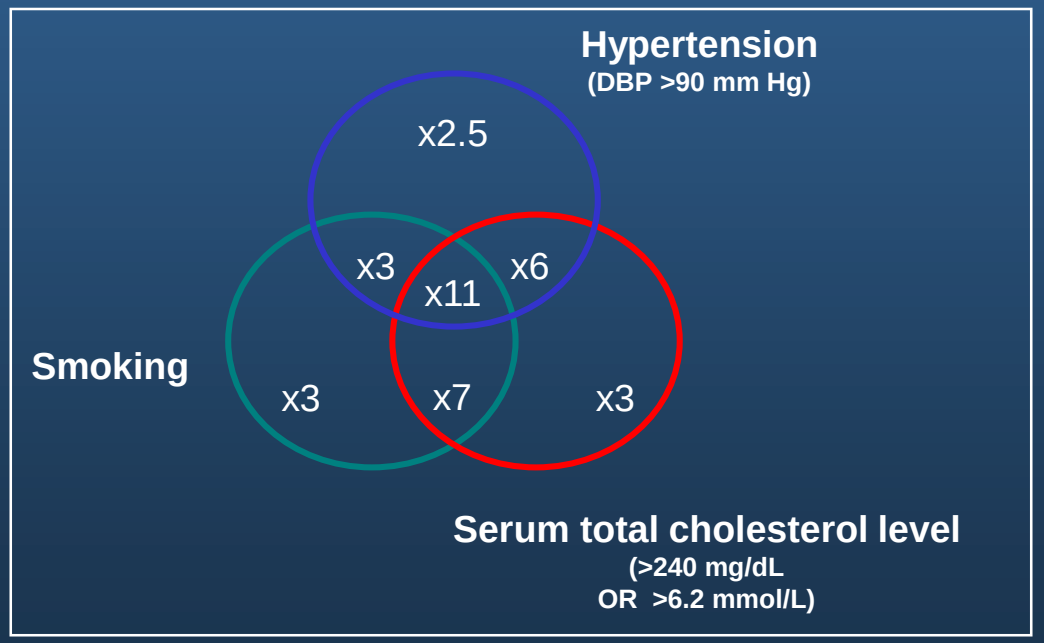
CVD DISEASE RISK FACTORS

Modifiable:

- Smoking
- Hypertension
- Diabetes mellitus
- Obesity
- Dietary factors
- Thrombogenic factors
- Sedentary lifestyle
- Dyslipidemia
  - Raised LDL-C
  - Low HDL-C
  - Raised TGs

Non-modifiable:

- Family history
- Age
- Gender



Adapted from Kannel WB et. al. *Am Heart J.* 1986. **12**:825-836.

Dyslipidemia/Lipid Disorders

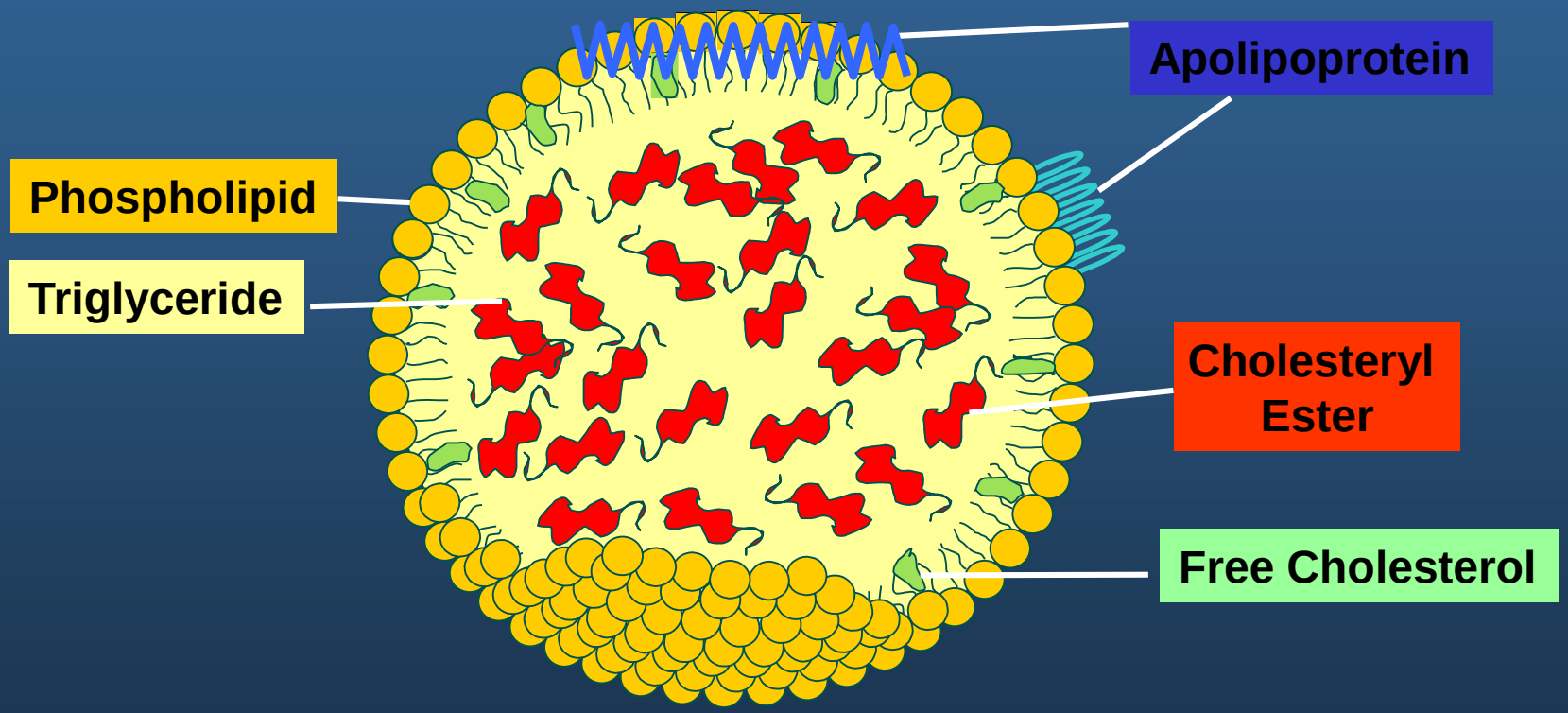
Hyperlipidemia or **Hyperlipoproteinemia**

- Involves abnormally elevated levels of any or all lipids and/or lipoproteins in the blood

- It is the most common form of dyslipidemia (which also includes any decreased lipid levels)

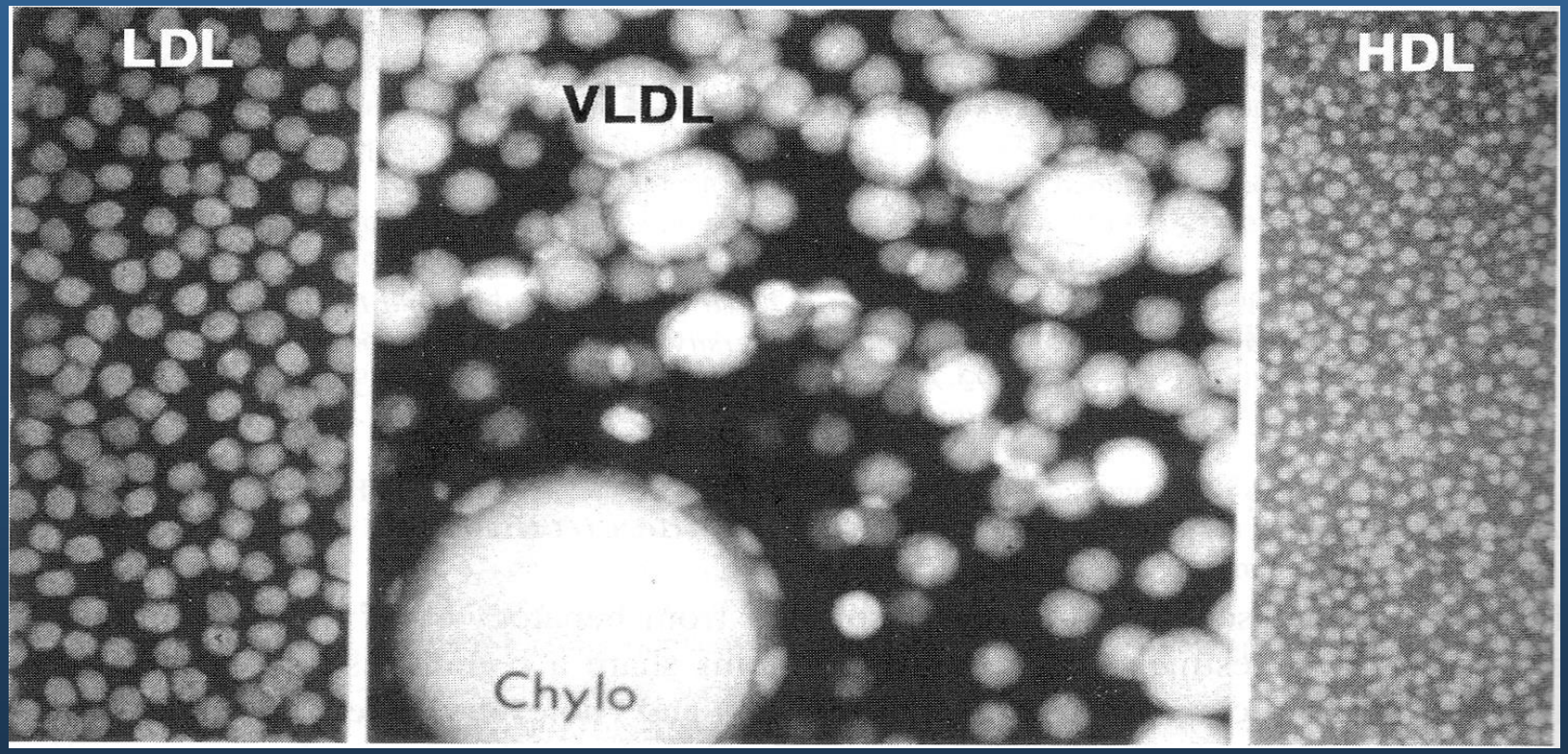
Lipoproteins

Spherical Microemulsion Particles



Major Lipoprotein Classes:

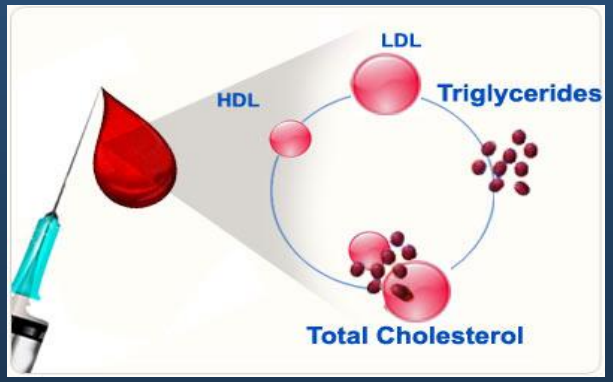
Chylomicron, VLDL, LDL, HDL



Biomarkers of Dyslipidemia and CHD Risk

Traditional risk markers

Total Cholesterol
LDL Cholesterol
HDL Cholesterol
Triglyceride



Non-Traditional risk markers

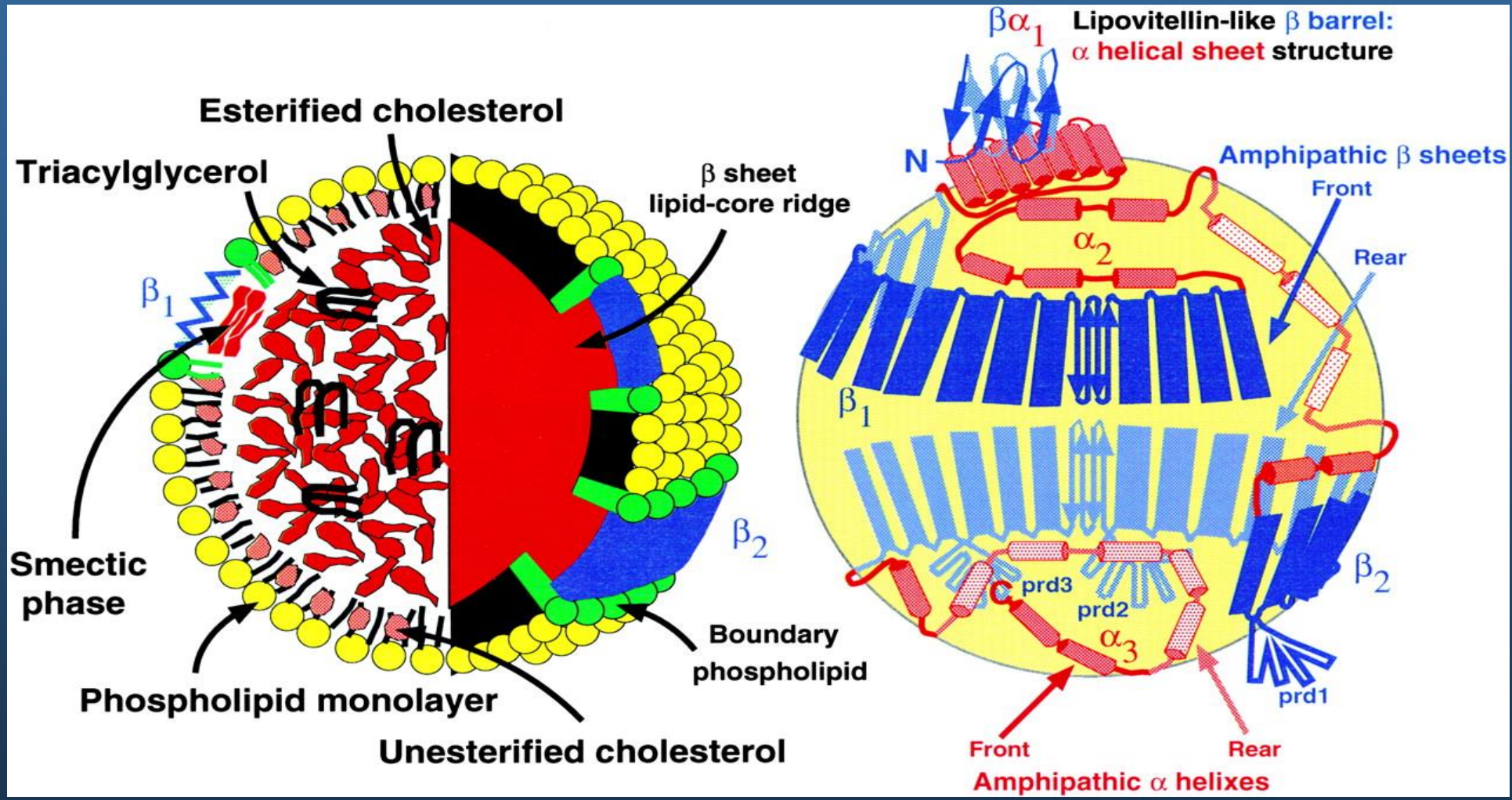
Non-HDL Cholesterol (calculated)
Apolipoprotein B
LDL particle size
C-reactive protein (CRP)
Lipoprotein(a)
Homocysteine
Fibrinogen
Plasminogen activator inhibitor
Cell adhesion molecules

LDL cholesterol

- Remains the cornerstone of dyslipidemia therapy
- Strongly associated with atherosclerosis and CHD events
- *A 10% increase results in a 20% increase in CHD risk*
- Most patients with elevated LDLc untreated

National Centre for Health Statistics. National Health and Nutrition Examination Survey (III)

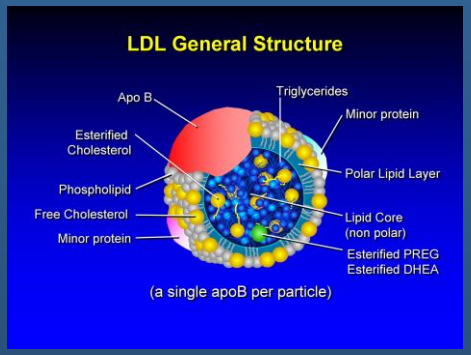
LDL Particle



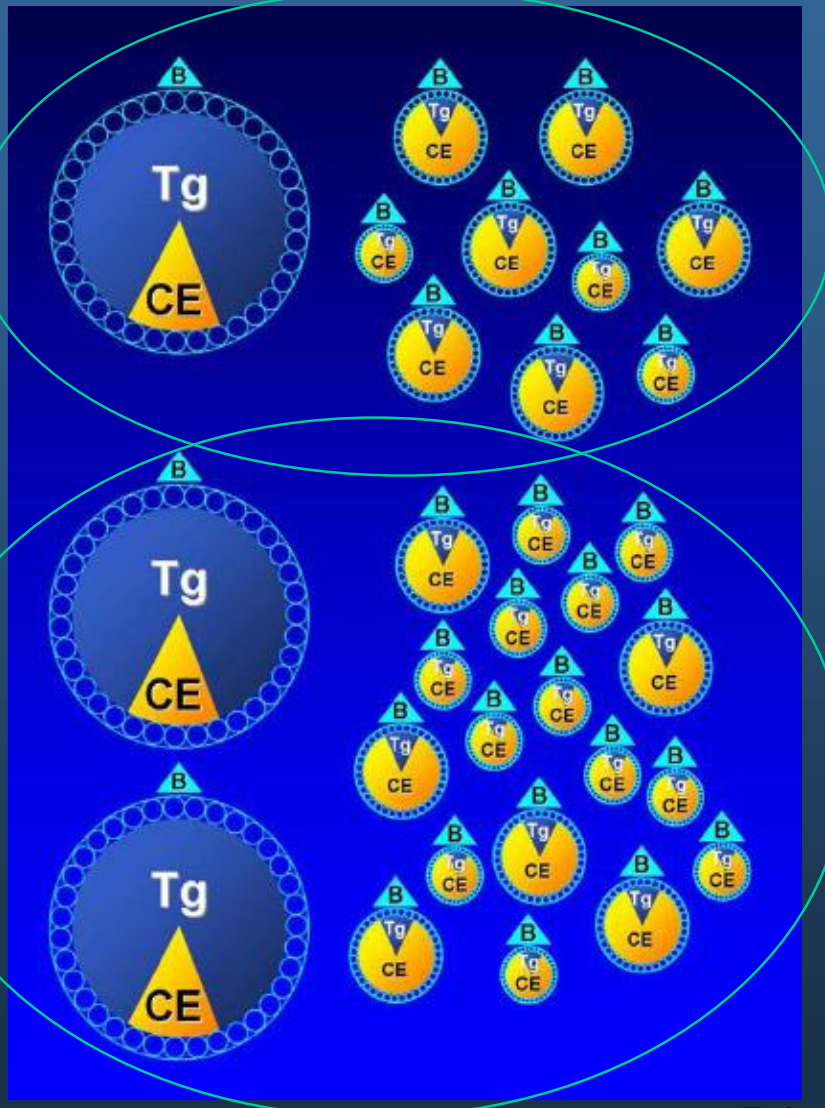
Segrest, J. P. et al. J. Lipid Res. 42:1346-1367

LDL Particles

- Each LDL particle has one molecule of ApoB protein
- ApoB Lipoprotein Particles in Healthy Subjects compared to those with Hypertriglyceridemic Hyper apoB Phenotype (the latter have higher number of LDL particles and higher plasma apoB)



Smaller/denser LDL particles = Higher CHD Risk

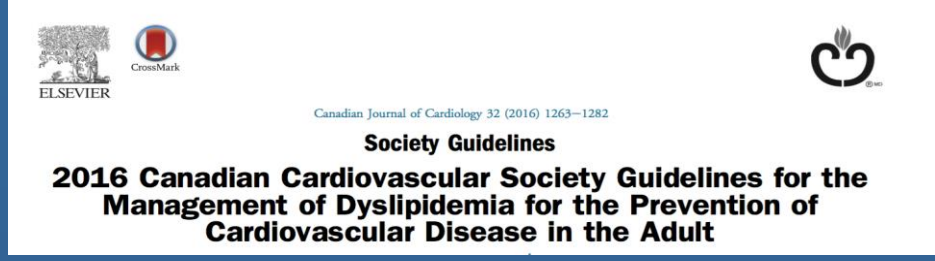


LIPID GUIDELINES

2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

Todd J. Anderson, MD, Jean Grégoire, MD, Glen J. Pearson, PharmD, Arden R. Barry, PharmD, Patrick Couture, MD, Martin Dawes, MD, Gordon A. Francis, MD, Jacques Genest, MD, Steven Grover, MD, Milan Gupta, MD, Robert A. Hegele, MD, David C. Lau, MD, PhD, Lawrence A. Leiter, MD, Eva Lonn, MD, G.B. John Mancini, MD, Ruth McPherson, MD, PhD, Daniel Ngui, MD, Paul Poirier, MD, PhD, John L. Sievenpiper, MD, PhD, James A. Stone, MD, PhD, George Thanassoulis, MD, Richard Ward, MD

Canadian Journal of Cardiology
Volume 32, Issue 11, Pages 1263-1282 (November 2016)
DOI: 10.1016/j.cjca.2016.07.510



Screening:

- Men and women ≥ 40 years of age
  - Earlier in South Asians, First Nations, those with CV risk factors (e.g. diabetes, hypertension, smoking, obesity)
- Fasting or non-fasting lipid panel (TC, LDL-C, HDL-C, TG, non-HDL-C), glucose, eGFR
  - Optional: apoB, urine albumin:creatinine ratio (if eGFR <60mL/min/1.73m^2, hypertensive, or diabetic)

WHO TO SCREEN

Men ≥40 years of age; women ≥40 years of age (or postmenopausal)

Consider earlier in ethnic groups at increased risk such as South Asian or First Nations individuals

All patients with the following conditions regardless of age:

- Clinical evidence of atherosclerosis
- Abdominal aortic aneurysm
- Diabetes
- Arterial hypertension
- Current cigarette smoking
- Stigmata of dyslipidemia (arcus cornea, xanthelasma or xanthoma)
- Family history of premature CVD*
- Family history of dyslipidemia
- Chronic kidney disease
- Obesity (BMI ≥30 kg/m^2)
- Inflammatory bowel disease
- HIV infection
- Erectile dysfuntion
- Chronic obstructive pulmonary disease
- Hypertensive diseases of pregnancy

Canadian Journal of Cardiology 2016 32, 1263-1282DOI: (10.1016/j.cjca.2016.07.510)

HOW TO SCREEN

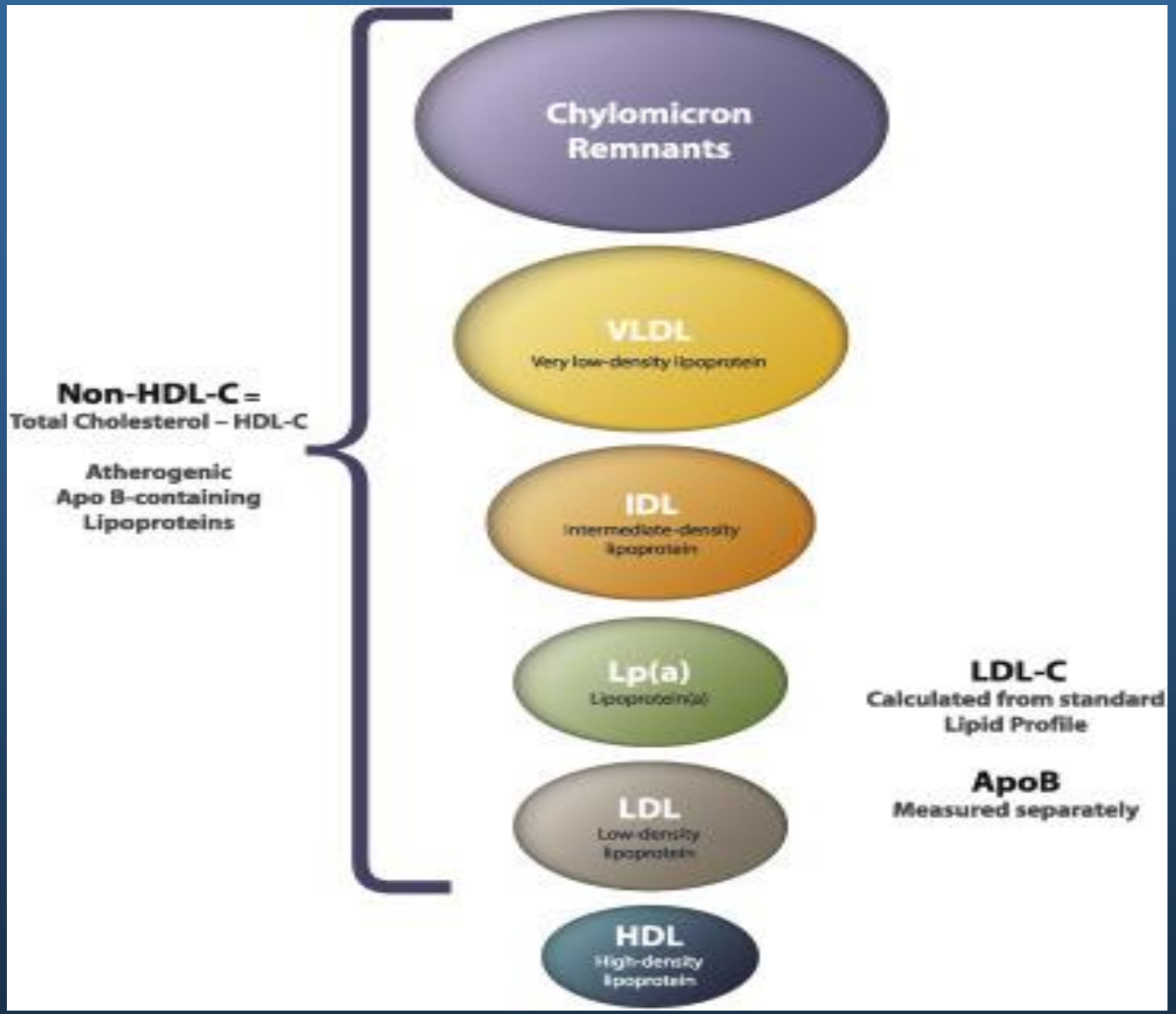
For all:

- History and physical examination
- Standard lipid panel (TC, LDL-C, HDL-C, TG)
- Non-HDL-C (will be calculated from profile)
- Glucose
- eGFR

Optional:

- ApoB
- Urine albumin:creatinine ratio
  (if eGFR <60 mL/min/1.73m^2, hypertension or diabetes)

NON-FASTING LIPID TESTING IS ACCEPTABLE


Chylomicron Remnants
VLDL
Very low-density lipoprotein
IDL
Intermediate-density lipoprotein
Lp(a)
Lipoprotein(a)
LDL
Low-density lipoprotein
HDL
High-density lipoprotein
Non-HDL-C =
Total Cholesterol – HDL-C
Atherogenic
Apo B-containing
Lipoproteins
LDL-C
Calculated from standard
Lipid Profile
ApoB
Measured separately

Recommended Adult (>18 years) Lipid Report

Analyte	Decision Limit	Result Comment
Total Cholesterol	<5.2 mmol/L	Treatment thresholds and targets based on the 2016 CCS Guidelines For patients ≥40 years, estimate risk using the modified Framingham Risk Score (FRS): **Low Risk (FRS < 10%)** Treatment advised if LDL-C ≥ 5.0 mmol/L Treatment target: ≥ 50% reduction LDL-C **Intermediate Risk (FRS 10 - 19%)** Treatment advised if LDL-C ≥ 3.5 mmol/L OR Non-HDL-C ≥4.3 mmol/L OR ApoB ≥ 1.2 g/L OR Men≥50 and women≥60 yrs with ≥1 additional CV risk factor Treatment targets: LDL-C ≤ 2.0 mmol/L OR decrease by ≥50% OR Non-HDL-C ≤2.6 mmol/L OR ApoB ≤ 0.8 g/L **High Risk (FRS ≥20% or presence of high risk features)** Treatment advised in all patients Treatment targets: LDL-C ≤2.0 mmol/L OR decrease by ≥50% OR Non-HDL-C ≤ 2.6 mmol/L OR ApoB ≤ 0.8 g/L Note: If non-fasting, triglycerides <2.0 mmol/L acceptable. Triglycerides >1.5 mmol/L, recommend to use non-HDL-C or ApoB as treatment target of choice If Triglycerides >4.5 mmol/L, recommend to measure lipids and lipoproteins fasted
HDL-C	>1.0 mmol/L	
LDL-C	<3.5 mmol/L	
Triglycerides	<1.7 mmol/L	
Non-HDL-C	<4.3 mmol/L	
Fasting (hours)	Record (h)	
ApoB	<1.2 g/L	Treatment thresholds and targets based on the 2016 CCS Guidelines **If ≥1.2 g/L** Treatment advised if Framingham Risk Score is Intermediate of High Treatment target for ApoB ≤ 0.8 g/L **If < 1.2 g/L** Treatment target for ApoB ≤ 0.8 g/L

Reference Intervals (RIs) vs Decision Limits (DLs)

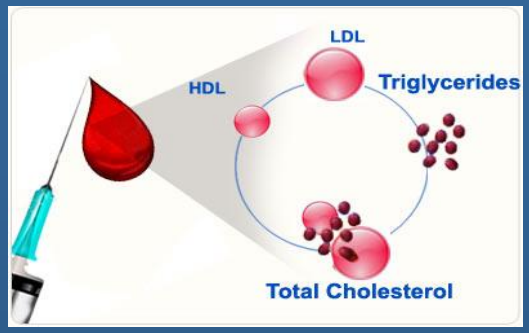
RIs and DLs are often listed in the same column on reports, which can confuse the basis of terminology and the distinction between the two

Reference Intervals: The range of laboratory test results expected in a healthy reference population (commonly defined as the 2.5^{th} and 97.5^{th} percentiles)

Decision Limits: Threshold values, in which values exceeding or falling below the threshold indicating the patient is at a significantly higher risk of a clinical outcome or satisfies criteria for diagnosis of a specific disease

"When decision limits determined by national or worldwide consensus exist, these limits, rather than reference intervals should be reported" – CLSI EP28-A3c

Fasting versus non-fasting lipid profiles



- Non-fasting lipids more representative of the normal state
- Increases convenience for patients
- Improve patient compliance
- Eliminates testing difficulty for patients who have trouble with prolonged fasting
- Samples received in lab throughout the day

Clinical Guidelines: *Fasting or Non-Fasting?*

- Danish Society for Clinical Biochemistry (2009)
- UK National Institute of Excellent (NICE, 2014)
- Canadian Cardiovascular Society Guidelines (2016)
- European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine (EAS/EFLM, 2016)
- 2019 ACC/AHA Guideline on the Primary Prevention o Prev f Cardiovascular Disease

Non-Fasting Recommended

Why have fasting lipid profiles been the standard?

- Concern related to increase in TGs postprandial
- LDL-c is calculated and was thought to be affected substantially by food consumption
- Randomized lipid lowering trials have used fasting measurements

Challenges of fasting lipid profiles

- Patient compliance
- Difficult for patients that have difficulty with prolonged fasting (Pediatrics, Geriatrics, …)
- Inconvenience
- Influx of samples early morning

Fasting versus non-fasting lipid profiles

- Non-fasting lipids more representative of the normal state
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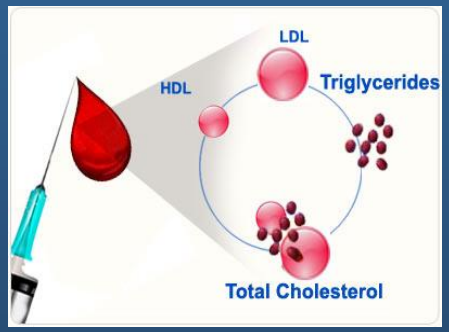


Perceived limitations to non-fasting lipids

- Fasting before a lipid profile assessment can provide more standardized measurements
- Non-fasting lipid profiles are less accurate
- Fasting has been the standard, there are no guidelines suggesting cutoffs in non-fasting samples

Can non-fasting lipid profiles predict CVD risk?

Table 3. Association of Triglyceride Levels With Incident Cardiovascular Disease According to Fasting Status

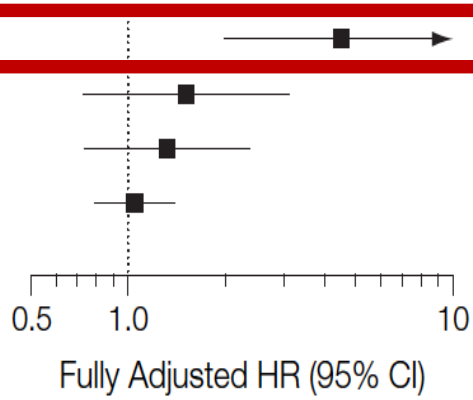
	Triglyceride Tertile 1	2	3	*P* Value for Trend	Per Unit Increase in Log(Triglyceride Level)[a]	*P* Value
	mmol/L		Fasting (n = 20118)			
Triglyceride level, mg/dL	≤ 1.02 ≤90	1.03-1.66 91-147	≥1.67 ≥148			
No. of participants	6590	6802	6726			
No. of events	126	262	398			
Event rate per 1000 person-y	1.74	3.52	5.48			
Model 1[b]	1 [Reference]	1.63 (1.31-2.02)	2.23 (1.82-2.74)	<.001	1.94 (1.71-2.22)	<.001
Model 2[c]	1 [Reference]	1.27 (1.02-1.59)	1.32 (1.03-1.68)	.09	1.34 (1.12-1.60)	.001
Model 3[d]	1 [Reference]	1.21 (0.96-1.52)	1.09 (0.85-1.41)	.90	1.11 (0.92-1.34)	.30
			Nonfasting (n = 6391)			
Triglyceride level, mg/dL	≤ 1.18 ≤104	1.19-1.92 105-170	≥1.93 ≥171			
No. of participants	2084	2174	2133			
No. of events	31	61	123			
Event rate per 1000 person-y	1.35	2.55	5.34			
Model 1[b]	1 [Reference]	1.48 (0.95-2.29)	2.53 (1.69-3.79)	<.001	2.12 (1.66-2.70)	<.001
Model 2[c]	1 [Reference]	1.31 (0.83-2.05)	1.94 (1.21-3.10)	.003	1.91 (1.37-2.67)	<.001
Model 3[d]	1 [Reference]	1.44 (0.90-2.29)	1.98 (1.21-3.25)	.006	1.67 (1.18-2.35)	.004

SI conversion factor: To convert triglyceride values to mmol/L, multiply by 0.0113.
[a] For example, corresponding to an increase in triglyceride level from 55 mg/dL to 150 mg/dL.
[b] Adjusted for age, blood pressure, smoking, and use of hormone therapy.
[c] Adjusted for covariates in model 1 plus total and high-density lipoprotein cholesterol.
[d] Adjusted for covariates in model 2 plus diabetes mellitus, body mass index, and high-sensitivity C-reactive protein.

Bansel et al, JAMA 2007

Figure 1. Association of Triglyceride Levels With Future Cardiovascular Events, Stratified by Time Since Last Meal

Time From Last Meal, h	No. of Participants	No. of Events	Hazard Ratio (95% Confidence Interval)
2 to <4	2797	98	4.48 (1.98-10.15)
4 to <8	2594	92	1.50 (0.72-3.13)
8 to <12	4846	177	1.31 (0.73-2.36)
≥12	15272	609	1.04 (0.79-1.38)

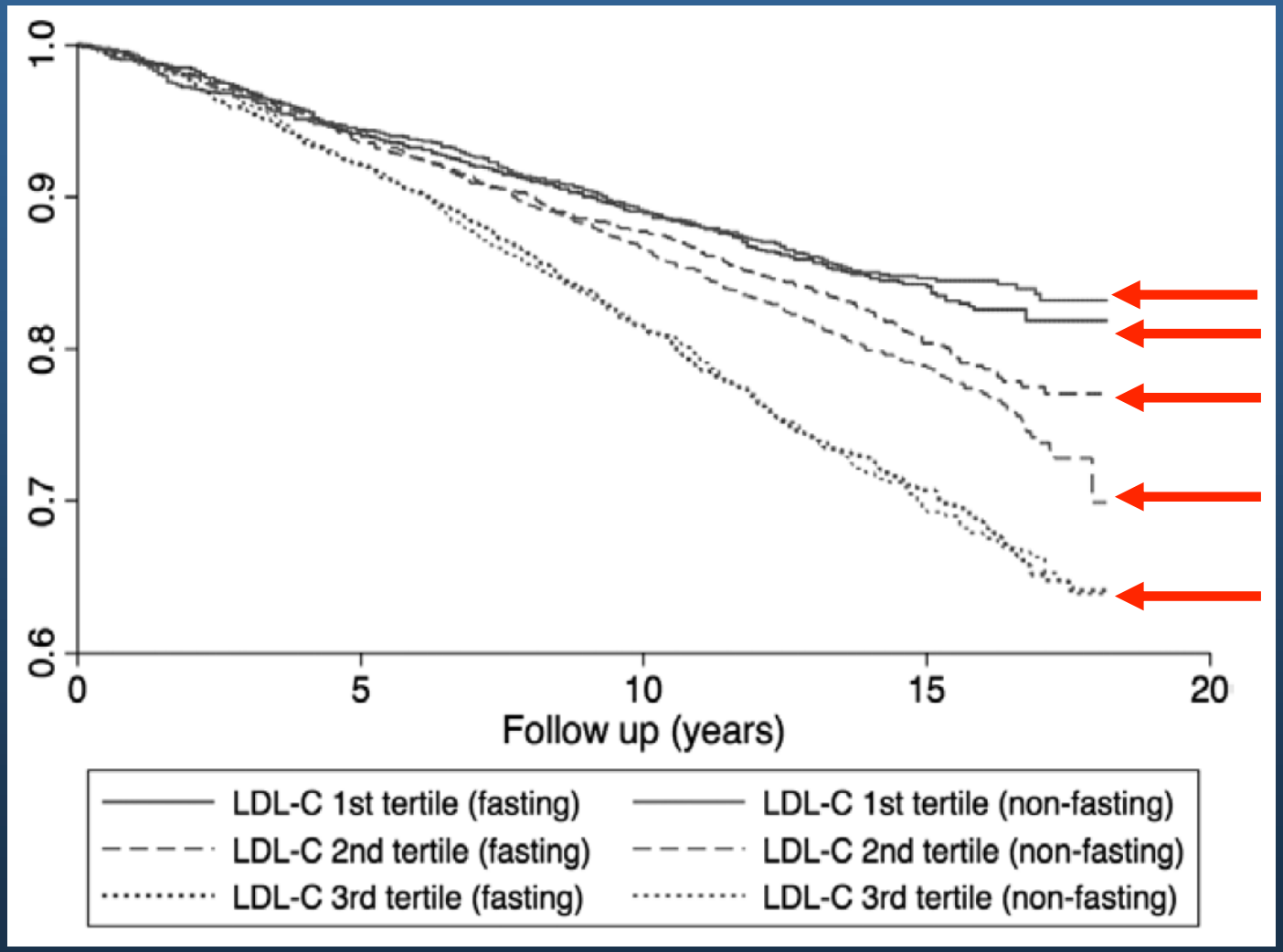


Hazard ratio (HR) and 95% confidence interval (CI) for highest vs lowest tertiles of triglyceride level (see Table 3 for values), adjusted for age, blood pressure, smoking, hormone use, levels of total and high-density lipoprotein cholesterol, diabetes mellitus, body mass index, and high-sensitivity C-reactive protein level.

Bansel et al, JAMA 2007

Triglyceride concentrations measured 4 h postprandially had the strongest association with cardiovascular events, with a fully adjusted

Fasting vs. Non-fasting LDLc levels and all cause mortality

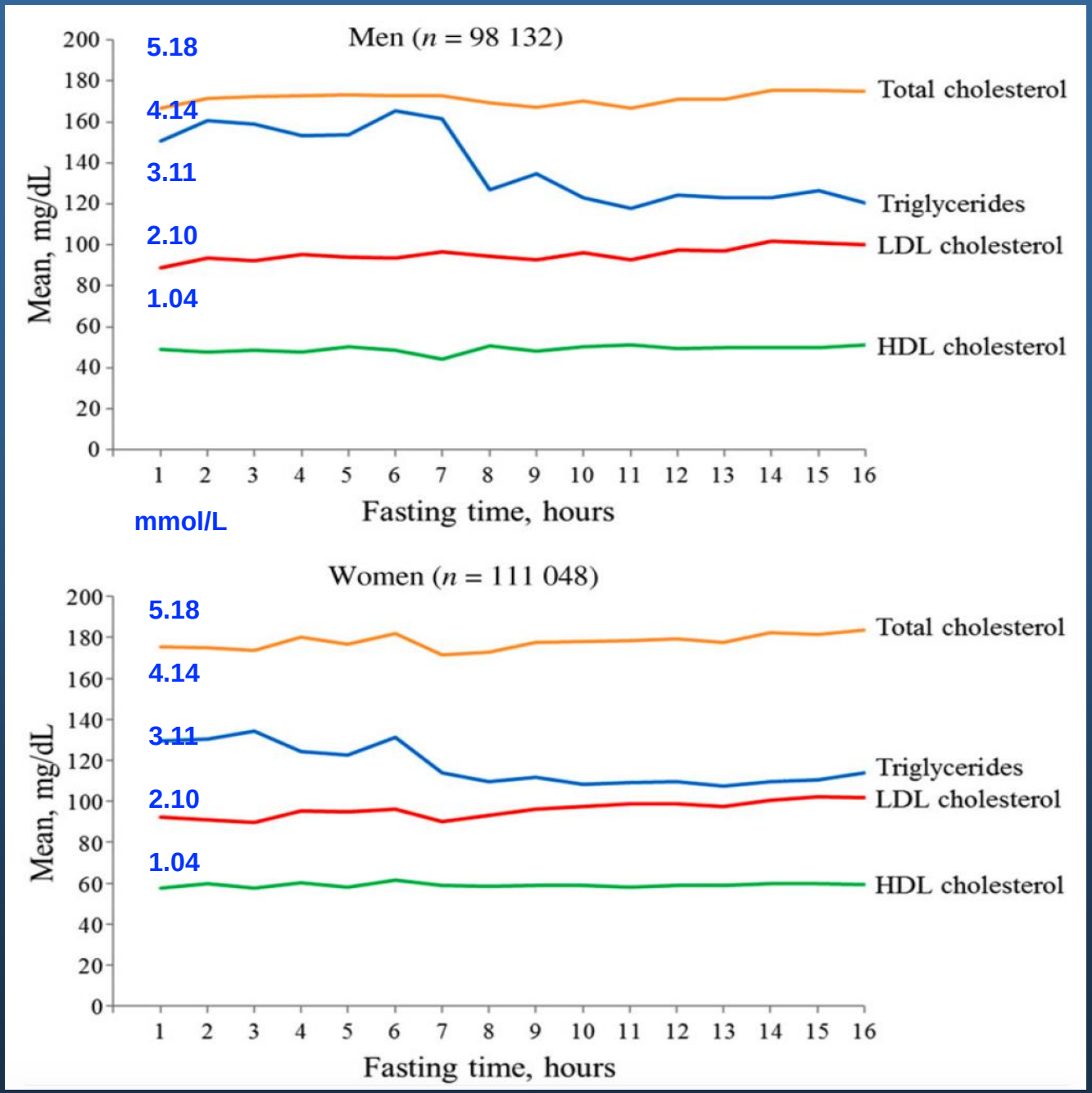


fasting and non-fasting

n= 16,161

Doran et al, Circulation. 2014; 130; 546

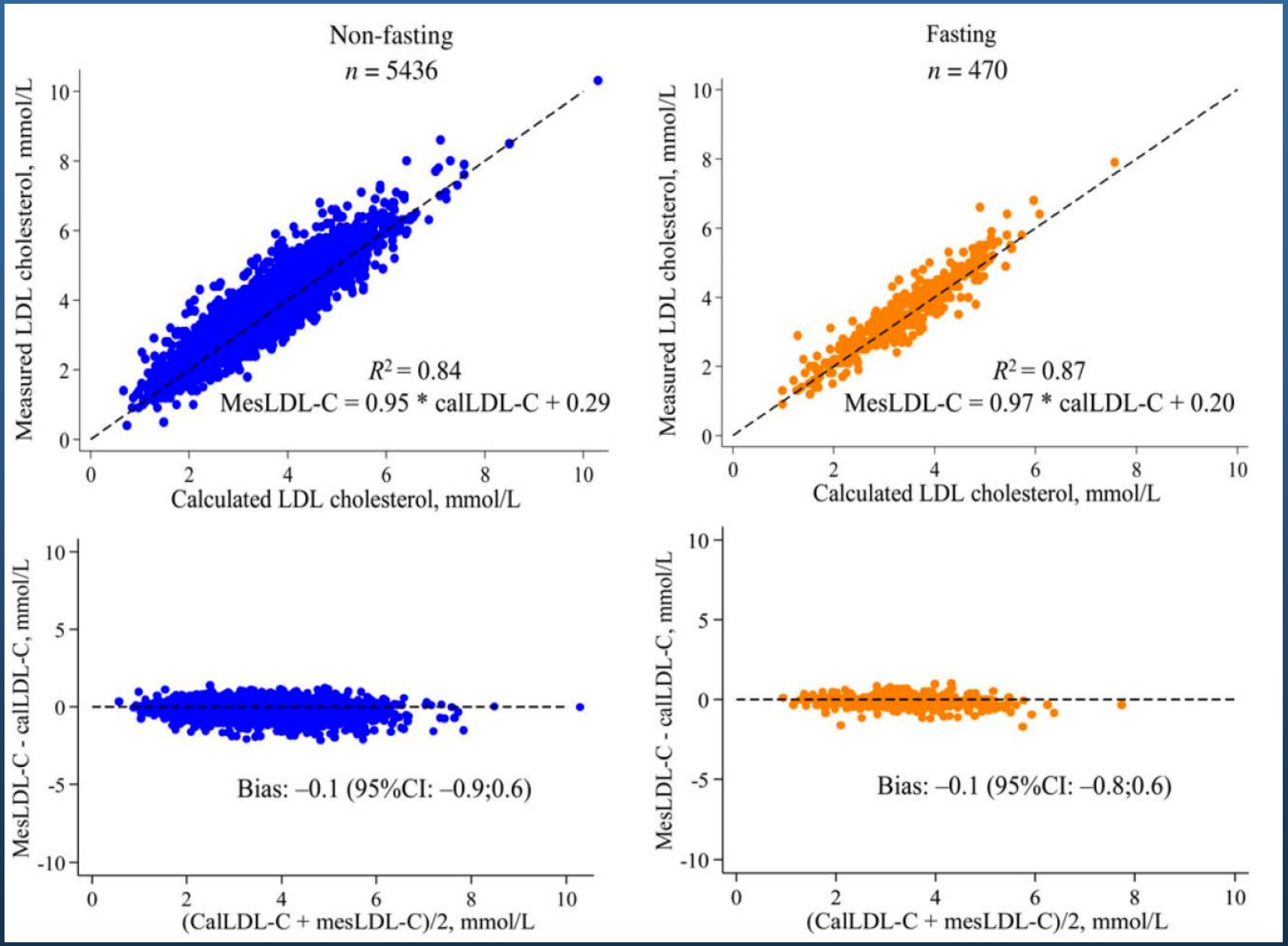
How do lipid profiles vary in fasting vs. non-fasting individuals?



Nordestgaard et al, Europ Heart J, 2016

Maximal Mean Changes 1-6 hr after consumption of a habitual meal as part of standard lipid profile

Study	Study population	TG	TC	LDL c	HDLc
Mora (2008)	Womens Health Study	**+16%**	**-1%**	**-5%**	nc
Langsted (2008)	Copenhagen General Population Study	**+21%**	**-4%**	**-6%**	**-6%**
Steiner (2011)	National Health and Nutrition Examination Survey	**+10%**	**-2%**	**-4%**	nc
Langsted and Nordestgaard (2011)	Men and Women without diabetes from the Copenhagen General Population Study	**+14%**	**-5%**	**-9%**	nc
Sidhu and Naugler (2012)	Calgary Laboratory Services	**+21%**	nc	**-4%**	nc



Nordestgaard et al, Europ Heart J, 2016

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THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Duration of Fasting, Serum Lipids, and Metabolic Profile in Early Childhood

Laura N. Anderson, PhD[1,2], Jonathon L. Maguire, MD[3,4,5,6], Gerald Lebovic, PhD[3,6], Anthony J. Hanley, PhD[4], Jill Hamilton, MD[4,5,7], Khosrow Adeli, MD[8], Brian W. McCrindle, MD[2,5], Cornelia M. Borkhoff, PhD[2,6,9], Patricia C. Parkin, MD[2,5,6,9], and Catherine S. Birken, MD[2,5,6,9], on behalf of The Applied Research Group for Kids! (TARGet Kids!) Collaboration*

Does fasting effect lipid profiles in young children?

Table I. Descriptive characteristics among children 0-6 years of age in TARGet Kids! (n = 2713)

Variables	First visit with blood testing
Age (mo), mean (SD)	34.6 ± 19.9
zBMI, mean (SD)	0.14 ± 1.09
Fasting duration (h), mean (SD)	1.87 ± 1.26
<1 h, no. (%)	478 (18%)
1 h, no. (%)	561 (21%)
2 h, no. (%)	805 (30%)
3 h, no. (%)	551 (20%)
4 h, no. (%)	250 (9%)
≥5 h, no. (%)	68 (2%)
Sex	
Female, no. (%)	1258 (46%)
Male, no. (%)	1455 (54%)
Maternal ethnicity	
European, no. (%)	1775 (68%)
East Asian, no. (%)	178 (7%)
Southeast/South Asian, no. (%)	237 (9%)
Other, no. (%)	411 (16%)
Weight	
Obese (zBMI >2.0), no. (%)	121 (5%)
Overweight (zBMI >1.0 and ≤2.0), no. (%)	379 (14%)
Normal (zBMI ≥ −2.0 and ≤1.0), no. (%)	2081 (79%)
Wasting (zBMI <−2.0), no. (%)	64 (2%)
Cholesterol (mmol/L), mean (SD)	4.02 ± 0.69
HDL (mmol/L), mean (SD)	1.26 ± 0.32
LDL (mmol/L), mean (SD)	2.16 ± 0.65
Non-HDL (mmol/L), mean (SD)	2.75 ± 0.68
Triglycerides (mmol/L), mean (SD)	1.31 ± 0.74
Insulin (pmol/L), mean (SD)	63.27 ± 56.58
Glucose (mmol/L), mean (SD)	4.63 ± 0.64
HOMA-IR, mean (SD)	1.97 ± 2.02

Conversion factors: To convert to mg/dL for cholesterol, HDL, LDL, and non-HDL divide by 0.0259; for triglycerides divide by 0.0113; and for glucose divide by 0.0555. To convert insulin to μIU/mL divide by 6.945.

Modified from Anderson et al, J Pediatr 2016

Table II. Regression of fasting duration in hours on laboratory outcomes unadjusted and adjusted for age, sex, maternal ethnicity, time of blood draw, and zBMI (n = 2713)

	Unadjusted		Adjusted*	
Outcome measures	Unadjusted coefficient	*P* value	Adjusted coefficient	*P* value
Total cholesterol (mmol/L)	0.006	.587	0.006	.629
HDL (mmol/L)	0.017	**.0004**	0.002	.708
LDL (mmol/L)	0.005	.630	0.013	.240
non-HDL (mmol/L)	–0.011	.261	0.004	.744
Triglycerides (mmol/L)†	–0.032	**.0009**	–0.016	.084

*Adjusted for age, sex, maternal ethnicity, time of blood draw, and zBMI.

Fasting duration has a very small impact on lipids in early childhood
Little evidence to support the need for fasting lipids

Modified from Anderson et al, J Pediatr 2016

Decision Limits/Cut-offs for Fasting versus Non-Fasting Lipid Levels

2016 European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine (EAS/EFLM) Guidelines

Recommended Decision Limits/Cut-Offs

Abnormal Concentrations	Non-fasting (mmol/L)	Fasting (mmol/L)	Change
Triglycerides	≥2	≥1.7	↑
Total Cholesterol	≥5	≥5	No change
LDLc	≥3	≥3	No Change
Remnant Cholesterol	≥0.9	≥0.8	↑
HDLc	≤1	≤1	No Change
non-HDLc	≥3.9	≥3.8	↑
Apo B	≥1.0 g/L	≥1.0 g/L	No Change

Concluding Remarks

- *Non-fasted state* represents the usual state during daytime in most people
- *Variation* in TGs, cholesterol and other lipids levels *is relatively small* with fasting vs. non-fasting profiles
- Non-fasting lipid profiles can *predict CVD events* as well as fasting
- However, non-fasting lipid profile testing is *NOT recommended for patients with hypertriglyceridemia*

ifcc
International Federation of Clinical Chemistry and Laboratory Medicine

LIPOPROTEIN PERSPECTIVES
A HEALTHCARE PROFESSIONAL RESOURCE