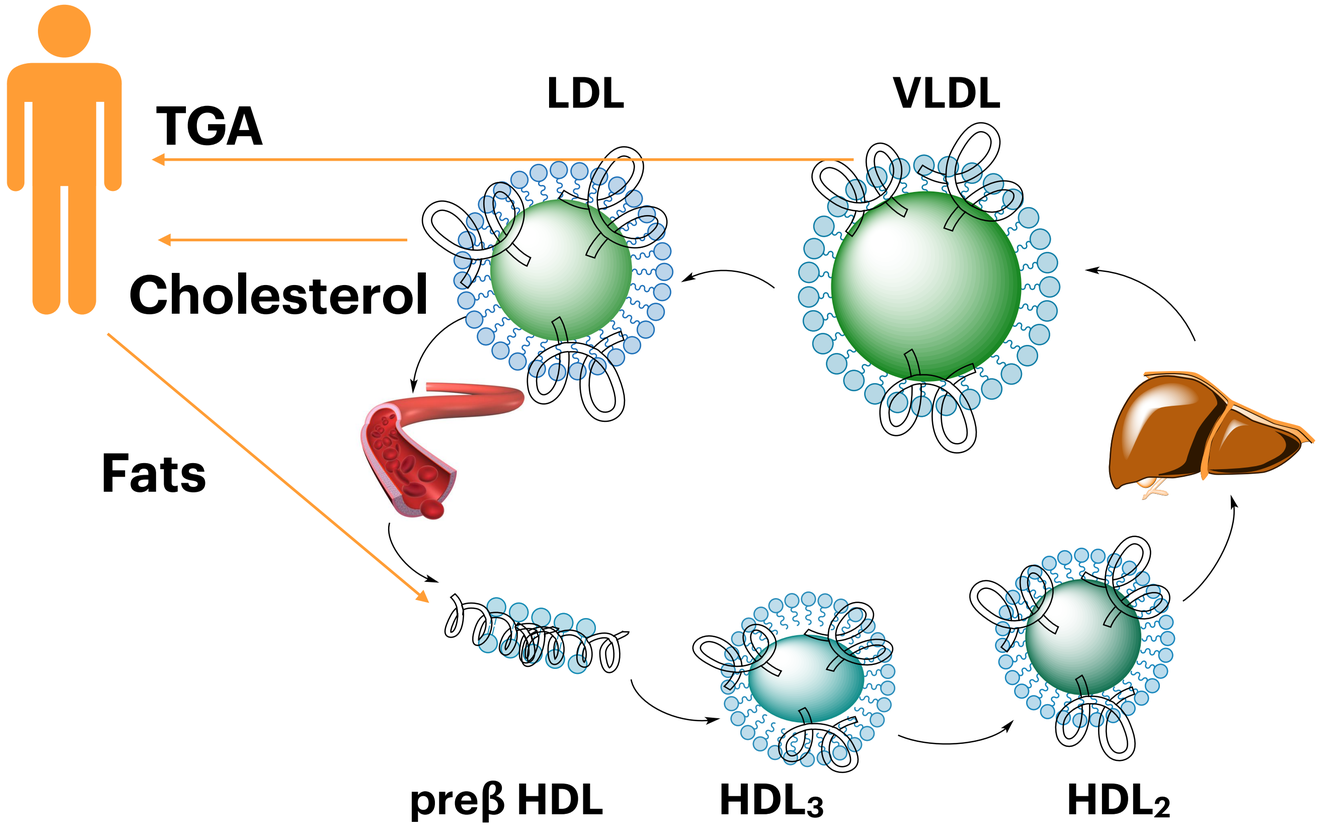
EXAMPLES OF HOW X-RAY AND NEUTRON SCATTERING CAN AIDE AT UPDATING MARKERS FOR ATHEROSCLEROSIS DEVELOPMENT

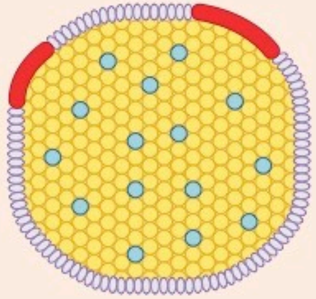
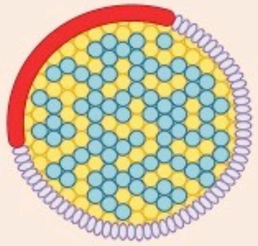
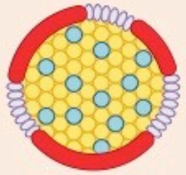
MARITE CARDENAS GOMEZ
MALMO UNIVERSITY
SWEDEN
MARITE.CARDENAS@MAU.SE

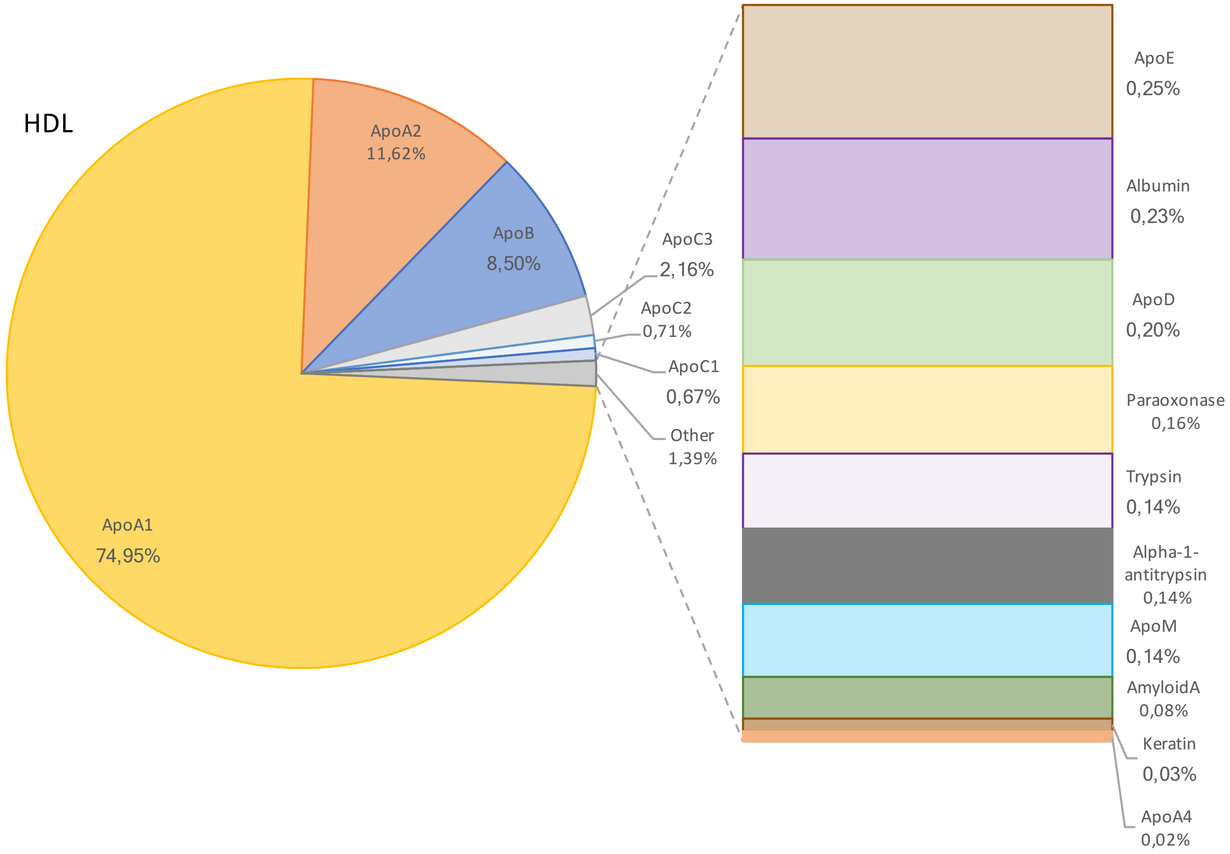
LIPOPROTEINS CARRY FAT IN THE BODY



LIPOPROTEIN COMPOSITION

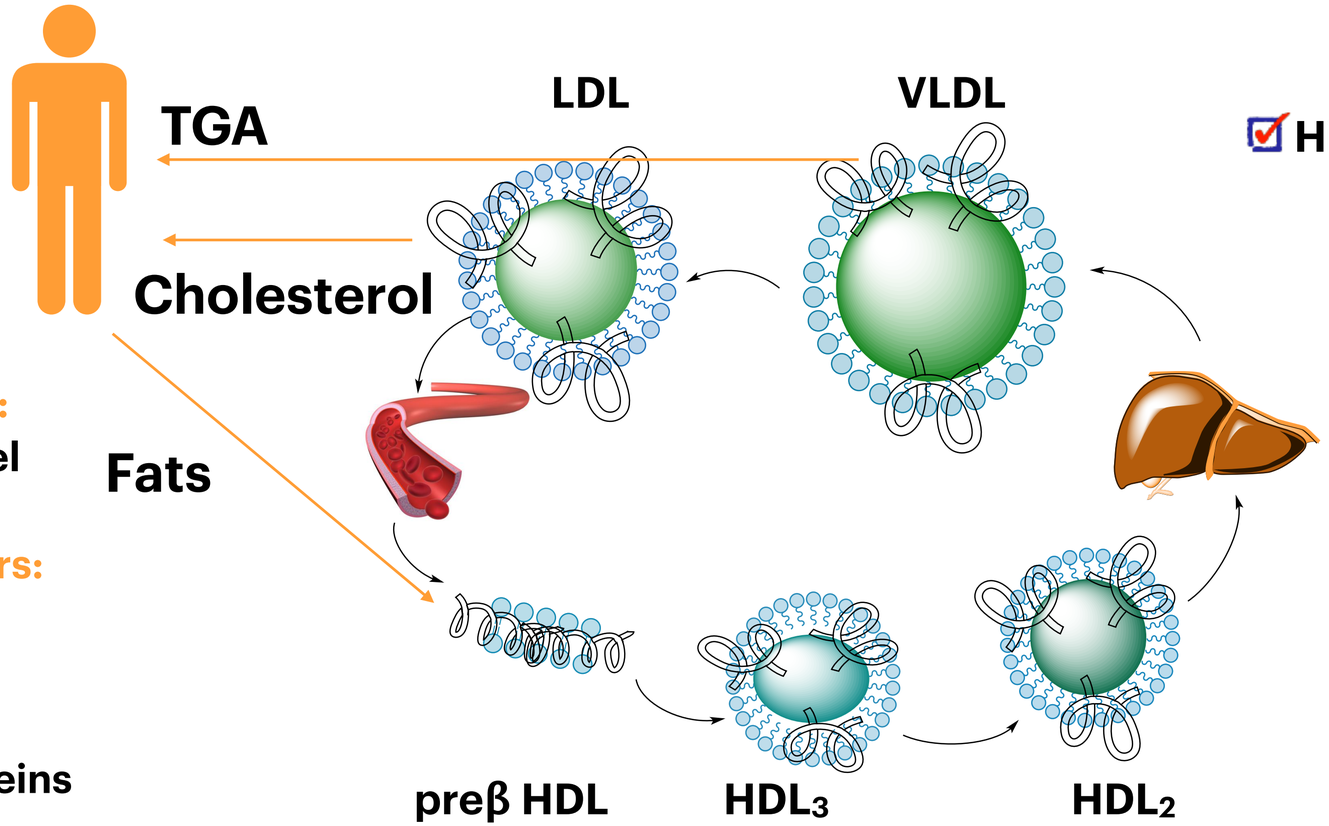
Not only the net composition in terms of fat vs protein is different, but also the exact lipid and protein specie is different between lipoprotein types

	Chylomicron	LDL	HDL
Diagram			
Triacylglycerol Cholesterol Phospholipid Apoprotein			
% Lipid			
• Triglyceride	**98**	15	10
• Cholesterol	~1	**60**	30
• Phospholipid	~1	25	60
% Protein			
	2	20	**50**



WHEN LIPID METABOLISM IS OFF BALANCE

Atherosclerosis becomes a problem



- ☑ The main killer of the world: ~17 million deaths/year
- ☑ Higher risk to develop a range of other diseases: Neurological, Diabetes, Liver and Kidney failure

Current clinical markers:

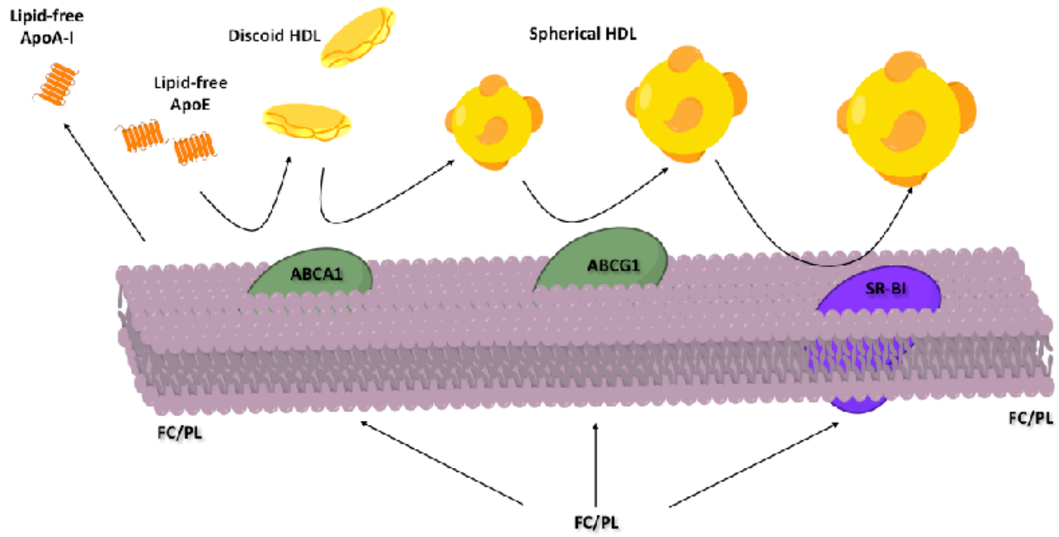
1. Total cholesterol level
2. Total LDL

Current further indicators:

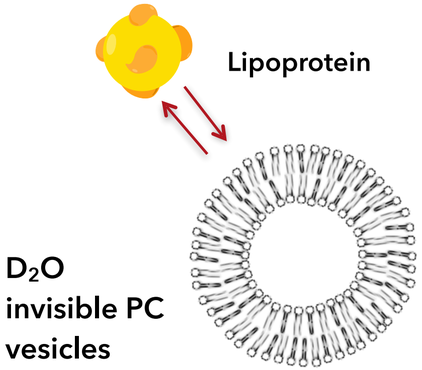
1. Specific enzymes
2. Oxidised species
3. HDL/LDL ratio
4. Specific apolipoproteins
5. LDL size profile
6. ...

MODELS TO FOLLOW THE TRANSPORT OF FATS

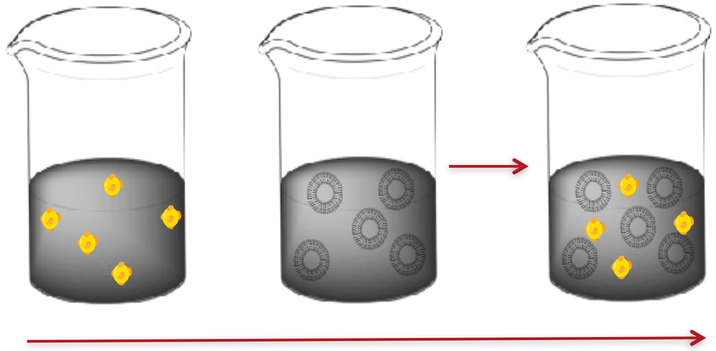
Dynamics of lipid exchange



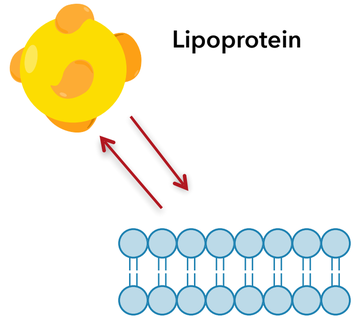
Time-resolved SANS



Structural and compositional changes within the lipoprotein

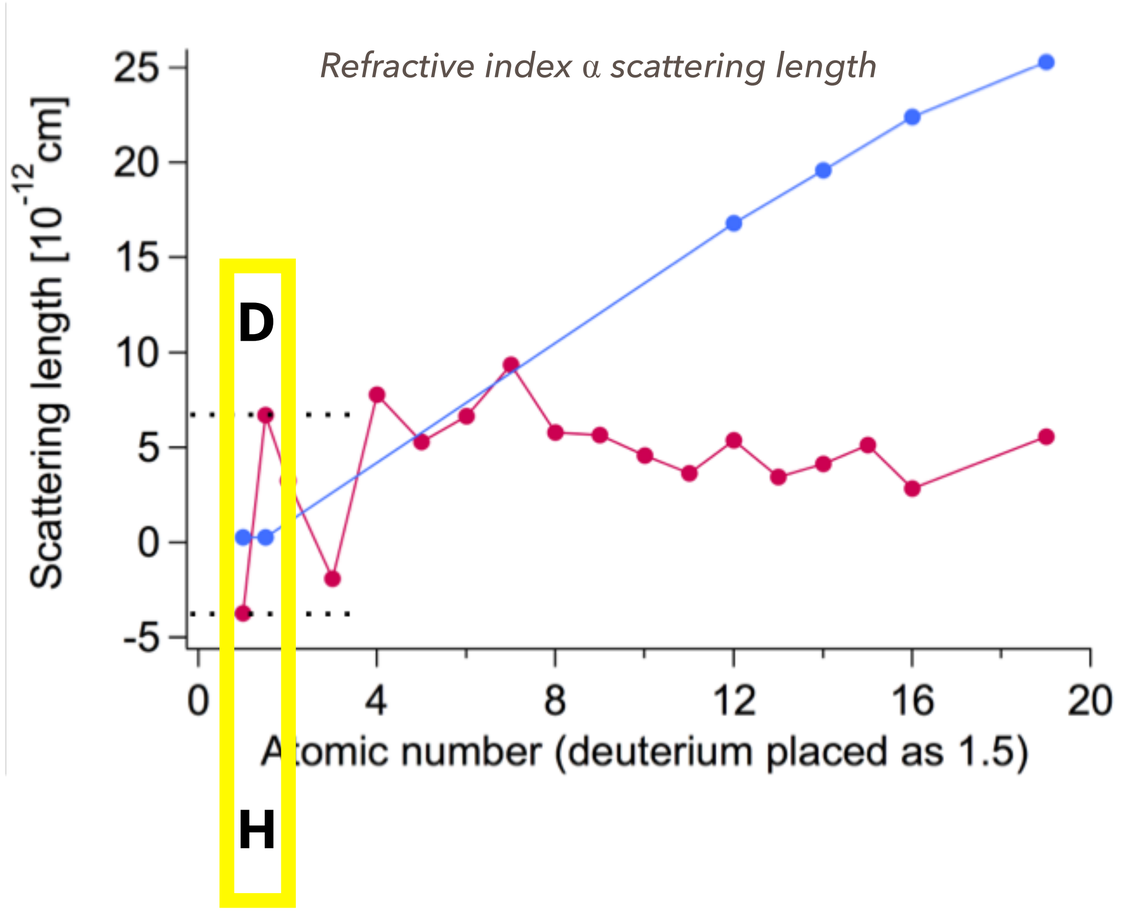


Time-resolved Neutron Reflection



Structural and compositional changes within the model cell membrane

NEUTRONS ARE COMPOSITIONAL SENSITIVE RADIATION



D rich

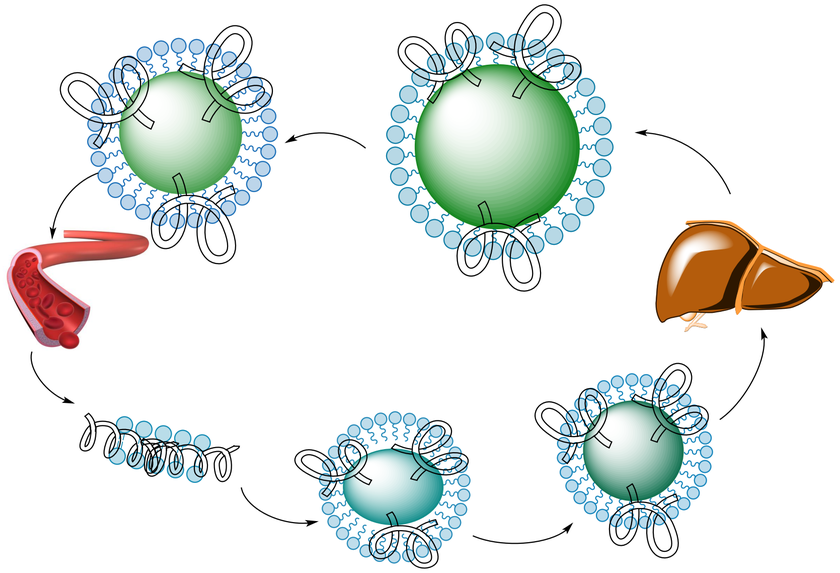
Most other bio-relevant atoms are in between the scattering length of D and H

H rich

Neutrons and X-ray scatter differently with atomic number: Can distinguish between atoms!

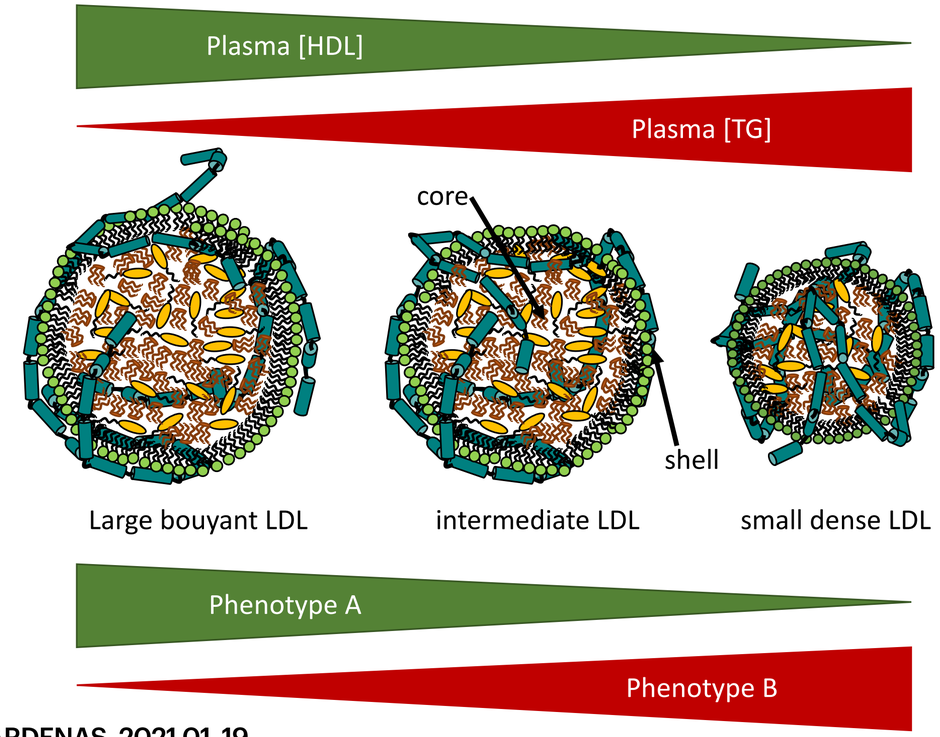
Deuteration of biomolecules is key: proteins, lipids, sterols, triglycerides....

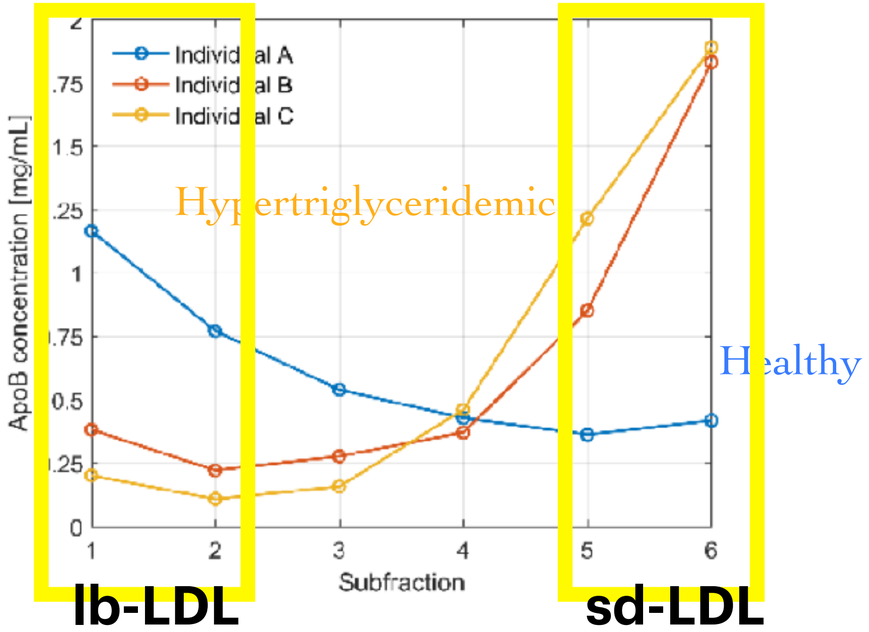
WHAT CAN WE LEARN ABOUT LIPOPROTEIN STRUCTURE?



LDL BEHAVIOR RELATES TO ITS SUBFRACTION PROFILE

- Serum LDL is correlated to the total serum cholesterol
- High LDL levels correlate with high risk for atherosclerosis

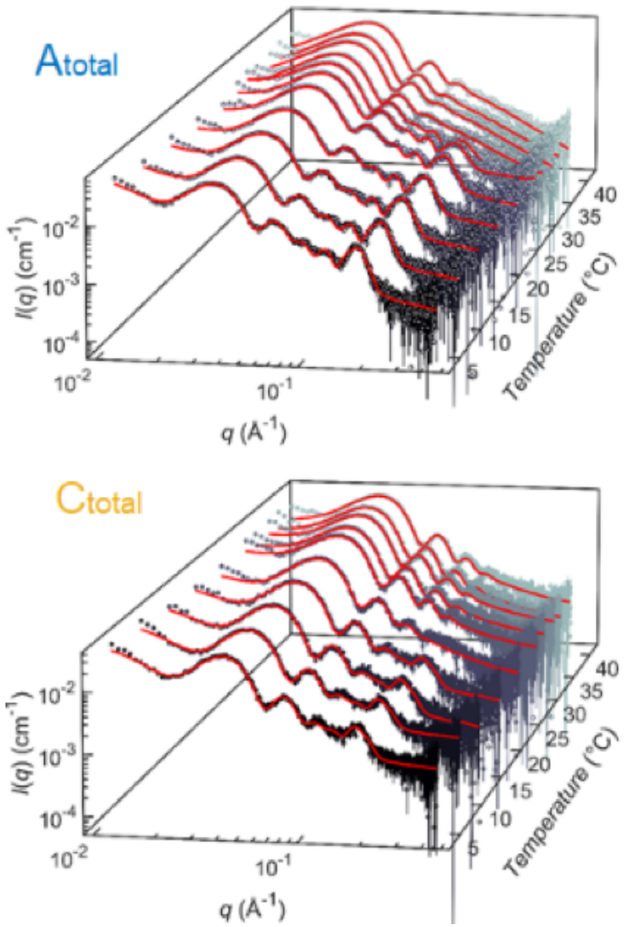


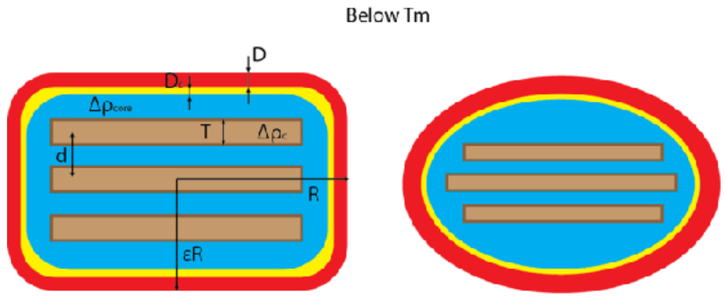


- Phenotype B LDL (high concentration of small dense LDL) correlates with high risk for atherosclerosis

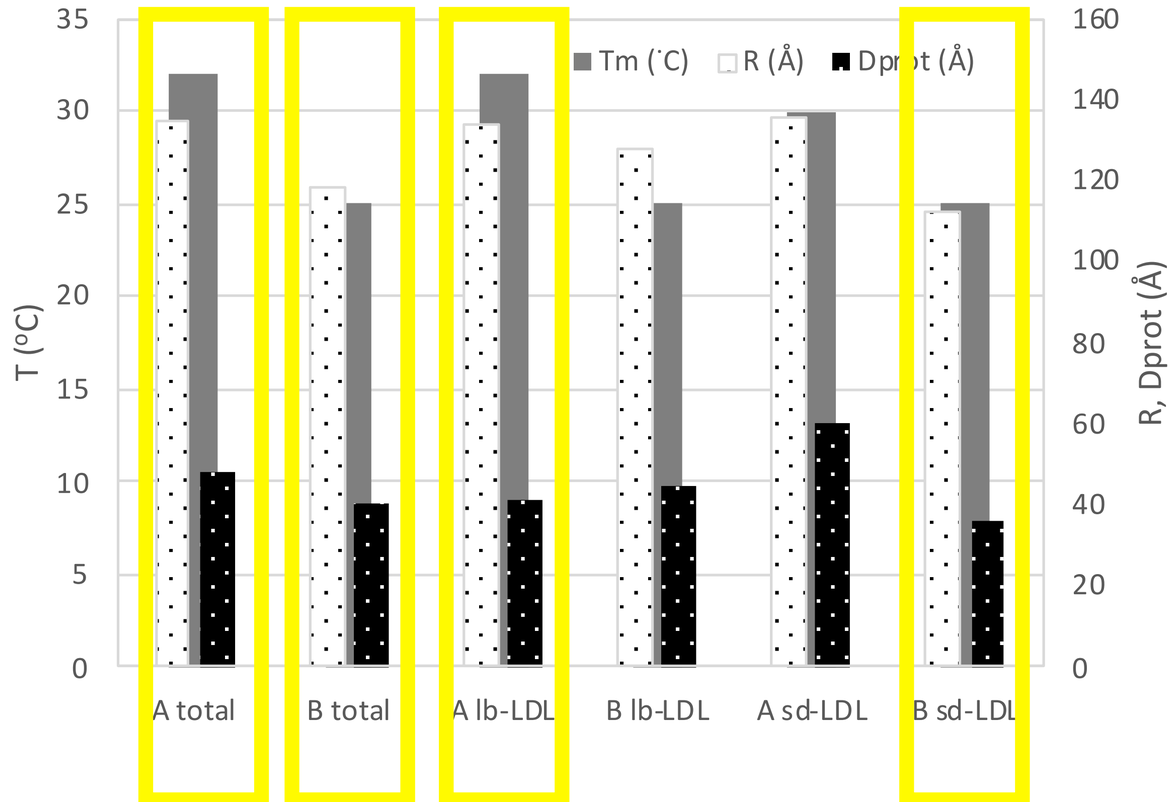
LDL BEHAVIOR RELATES TO ITS SUBFRACTION PROFILE

SAXS



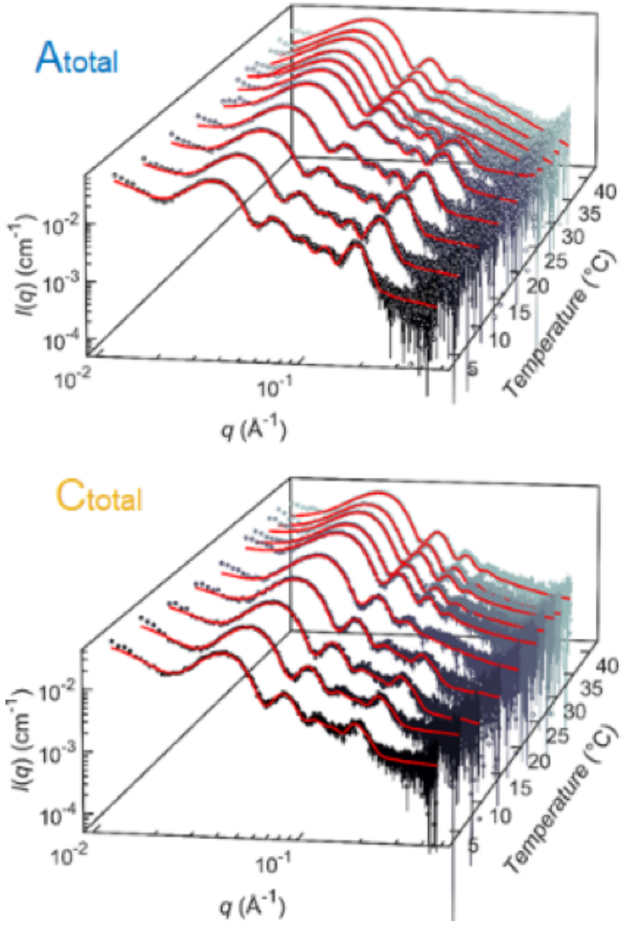


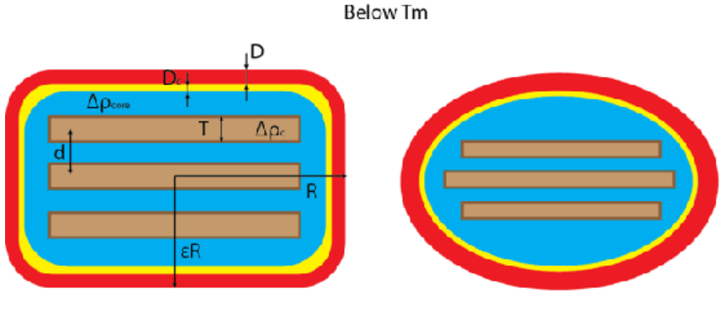
Maric et al. ACS Nano 2017 11, 1080



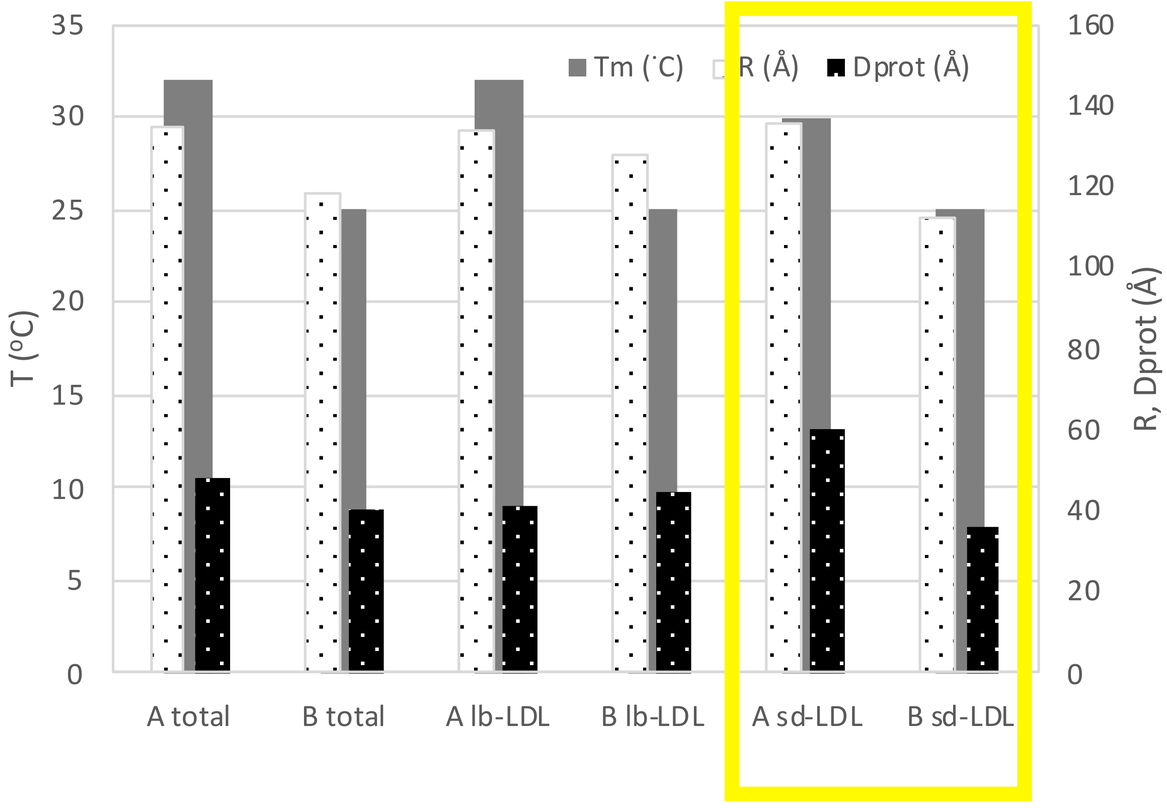
LDL BEHAVIOR RELATES TO ITS SUBFRACTION PROFILE

SAXS





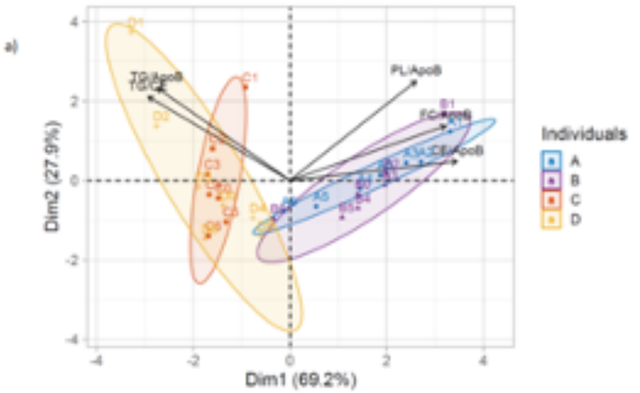
Maric et al. ACS Nano 2017 11, 1080

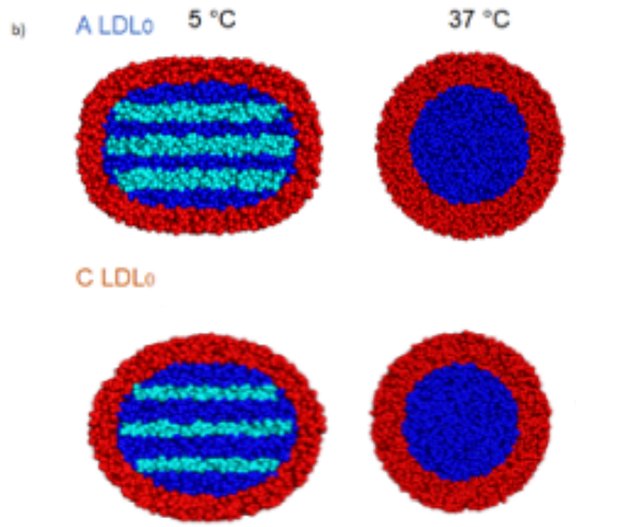


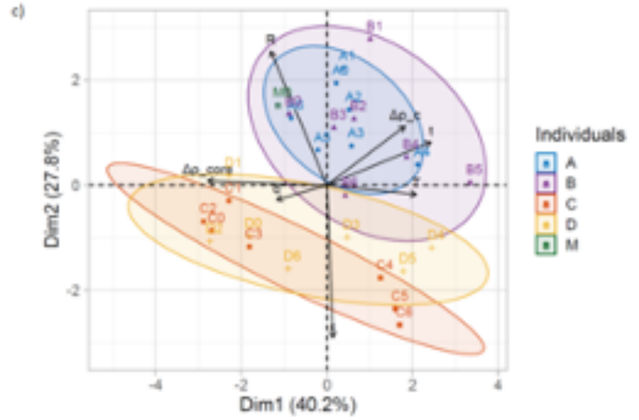
SAXS CAN DETERMINE WITH ACCURACY THE LDL PHENOTYPE FROM THE TOTAL LDL FRACTION,

BUT IT IDENTIFIED DIFFERENCES IN STRUCTURE FOR SMALL DENSE LDL BETWEEN HEALHTY AND HYPERTRYGLICERIDEMIC INDIVIDUALS

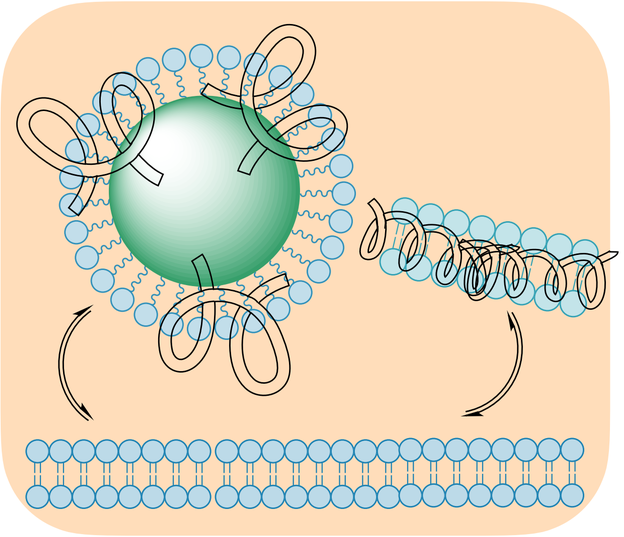
Jakabauskas et al 2020 NanoMedicine



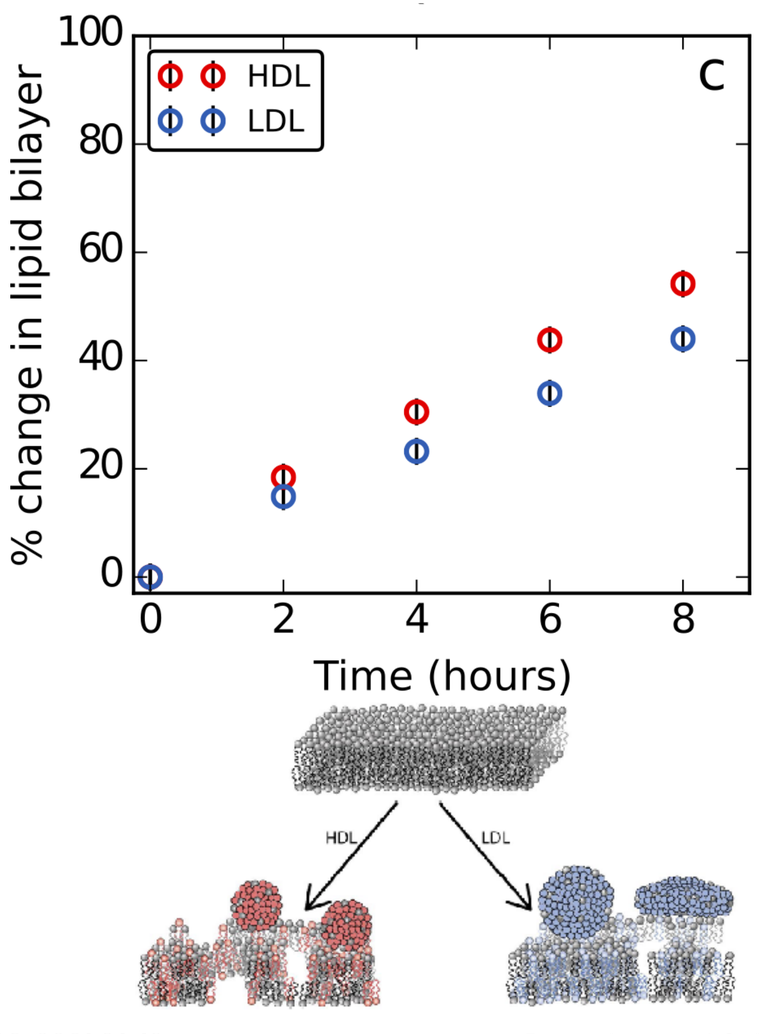


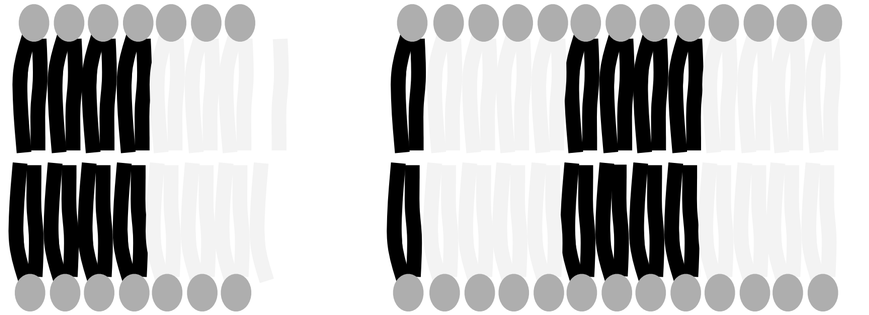


HOW CAN NEUTRON REFLECTION MEASURE LIPID EXCHANGE TO QUANTIFY LIPID REMOVAL AND LIPID DEPOSITION INDEPENDENTLY?



AVERAGE LIPID EXCHANGE





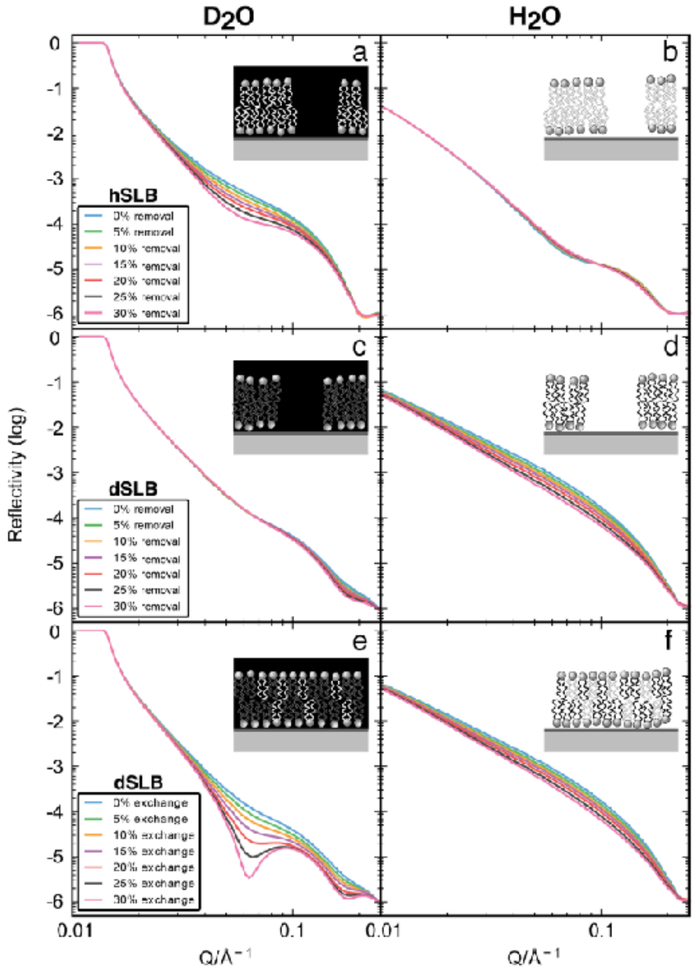
Scattering length density (SLD) of the lipid core is proportional to the composition in terms of lipid tails, but also to the number of solvent filled- defects

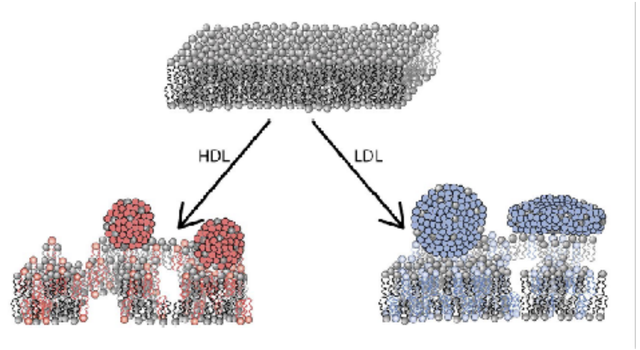
average lipid exchange =

$(SLD_{prior\ LDL}-SLD_{after\ LDL})/ SLD_{prior\ LDL}$

Browning et al Sci Reports 2017 7, 7478

EXTENT OF LIPID EXCHANGE





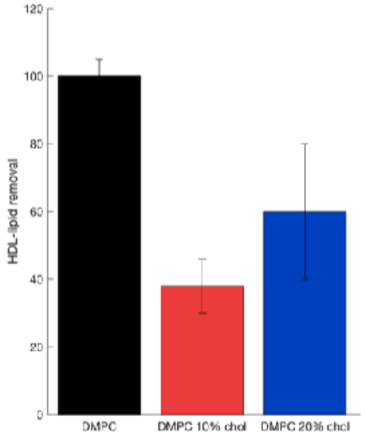
On dDMPC	HDL	LDL
Hydrogenation in bilayer after addition	32 %	28 %
Water in tail region after addition	13 %	0 %
Change in bilayer thickness	+3 Å	+ 3 Å
% LP coverage	4 % / 44Å	2 % / 170Å

Browning et al Sci Reports 2017 7, 7478

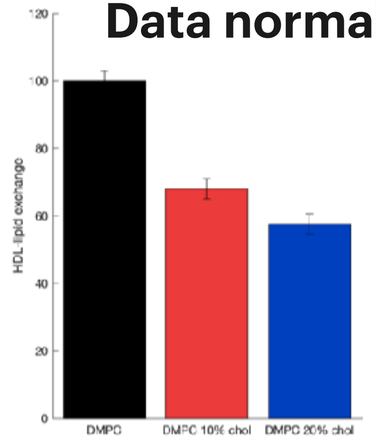
EFFECTS OF CHOLESTEROL AND SATURATED VS UNSATURATED FATS ON LIPOPROTEIN CAPACITY TO EXCHANGE FATS

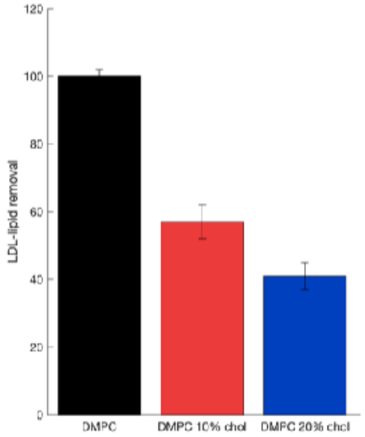
Matchout cholesterol developed

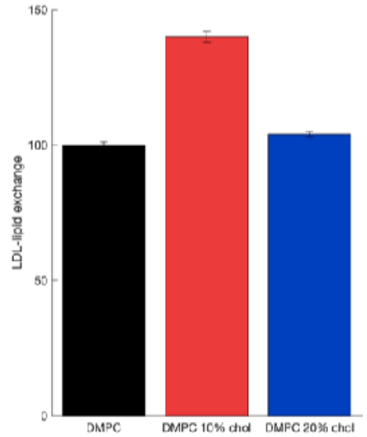
Waldie *et al Sci Rep 2019*

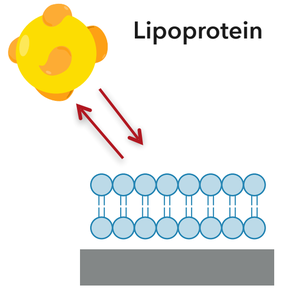


Data normalised to DMPC







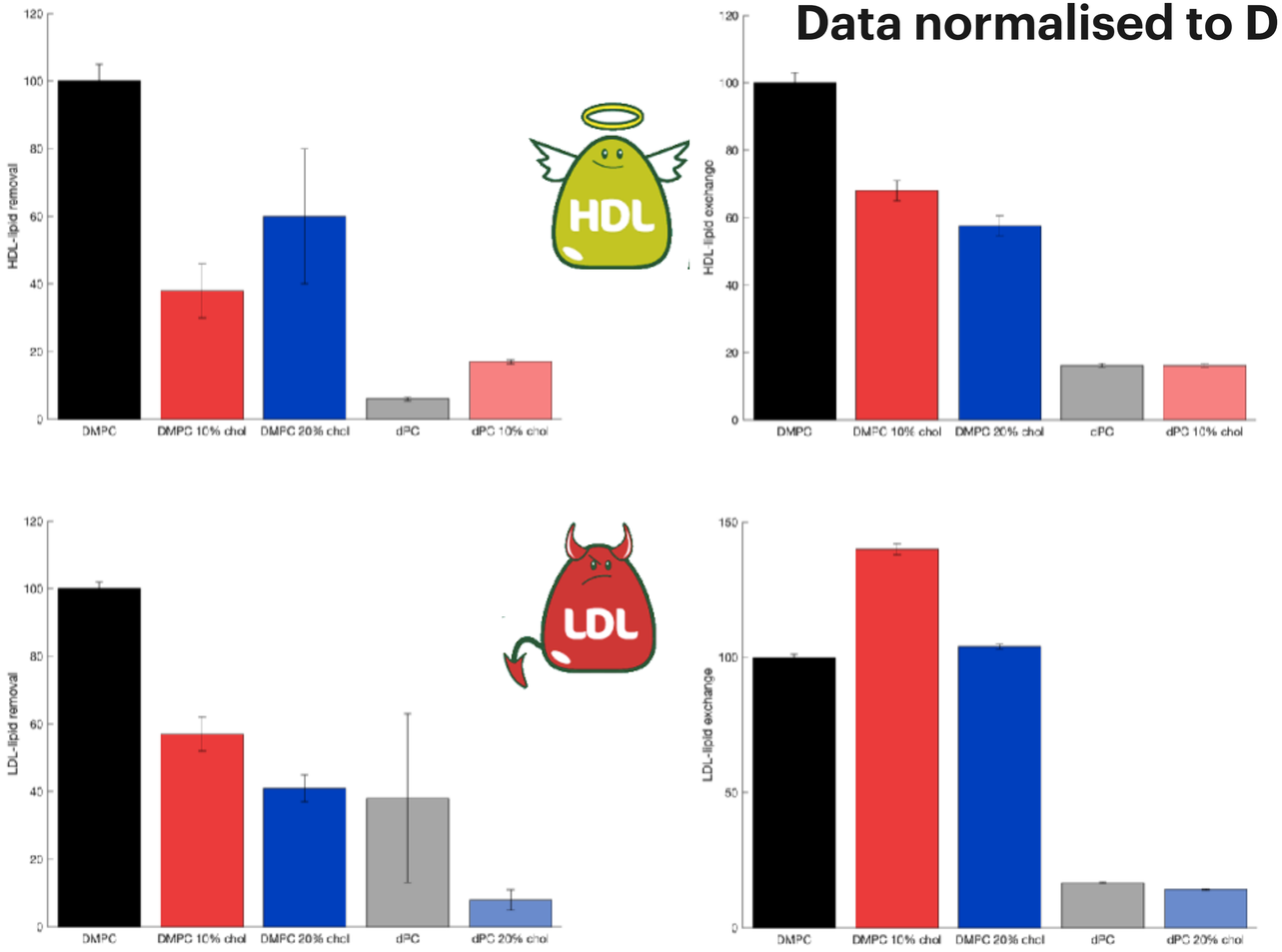


Waldie *et al BBA Cell Mol. Biol. Lipids 2020*

EFFECTS OF CHOLESTEROL AND SATURATED VS UNSATURATED FATS ON LIPOPROTEIN CAPACITY TO EXCHANGE FATS

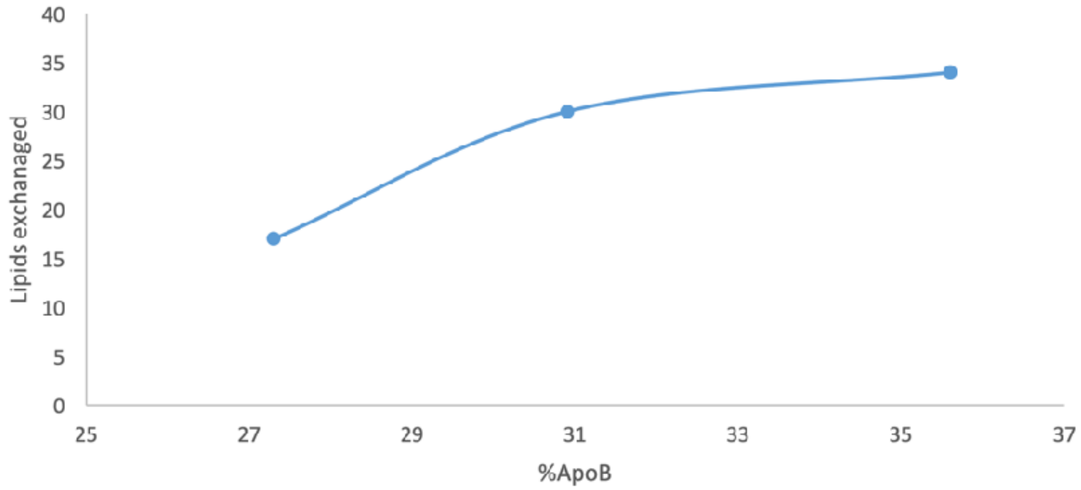
Cholesterol decreases the ability of lipoproteins to remove and deposit fats, with more marked effects for HDL

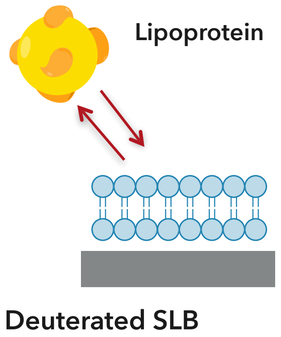
Unsaturated fats are not taken up or exchanged significantly by HDL (or LDL though fat removal is less affected)



Waldie *et al BBA Cell Mol. Biol. Lipids 2020*

DOES LDL COMPOSITION HAVE AN EFFECT ON ITS CAPACITY TO EXCHANGE FATS?





The denser the LDL fraction, the more lipids are exchanged!

Prevalence of denser LDL particles are correlated with pro-atherogenic properties

Waldie *et al BBA Cell Mol. Biol. Lipids 2020*

IN SUMMARY

1. Lipoproteins are nano-emulsions composed of lipids and proteins
2. The functionality of lipoproteins depends on both the lipid and protein cargo
3. SAXS excels at determining the structure of LDL particles and could serve as a basis to predict the LDL phenotype
4. TR-NR and TR-SANS are complementary techniques that allow mapping the transport of fats by lipoproteins
5. Biomolecular DEUTERATION is key to unravel such structural and kinetic aspects

ACKNOWLEDGEMENTS

COLLABORATORS, STUDENTS AND FUNDING

Prof. Trevor Forsyth (ILL)

Dr. Michael Haertlein (ILL)

Dr. Tamim Darwish (ANSTO)

Dr. Luke Clifton (STFC)

Dr. Martin Jansen (UKF)

Prof. Martin Malmsten (UU/KU)

Prof. Gunilla Fredrikson (LU)

Dr. Eva Bengtsson (LU)

Prof. Jan S. Pedersen (LU)

Sarah Waldie (PhD student, graduated on 2020)

Yubexi Correa (PhD student, to graduate on 2023)

Tania K. Lind (Postdoc)

Selma Maric (Postdoc)

Kathryn Browning (Postdoc)

Dainius Jakubauskas (Postdoc)

Vetenskapsrådet

Interreg
Öresund-Kattegat-Skagerrak
ESS & MAX IV: Cross Border Science and Society
This project is sponsored by the European Regional Development Fund

Crafoordska stiftelsen
GRUNDAD AV HOLGER CRAFOORD 1980

NEUTRONS FOR SOCIETY