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ROVIRA I VIRGILI

*ciberdem*

Spanish Biomedical Research Centre in  
Diabetes and Associated Metabolic Disorders

# Metabolomics and Personalized Medicine

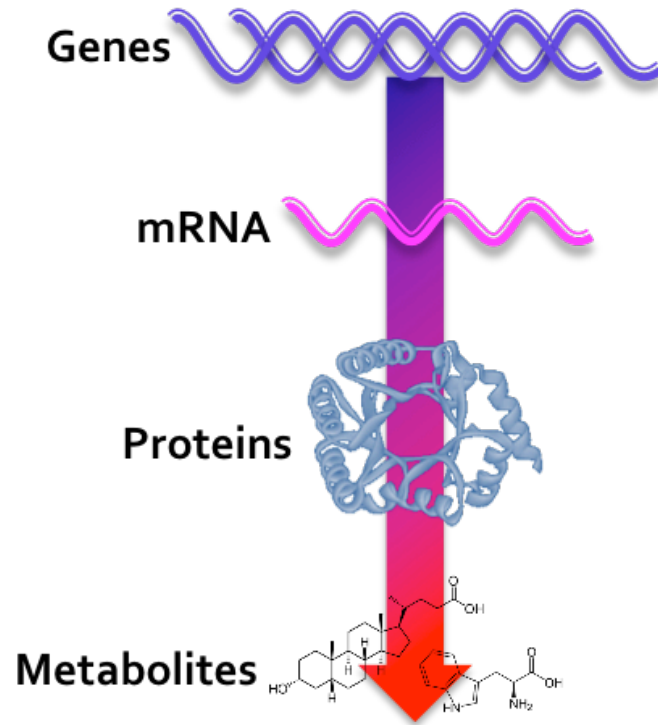
FEAM Spring Conference  
Bern, May 20<sup>th</sup> 2016

Oscar Yanes Ph.D.

Genome

Transcriptome

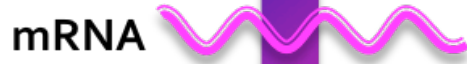
Proteome



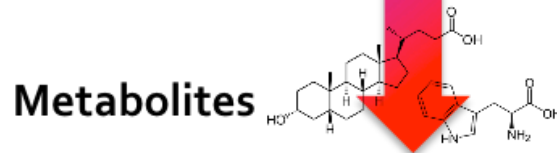
Genome



Transcriptome

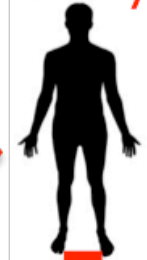
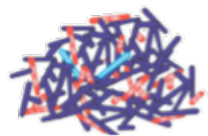


Proteome



Phenotype

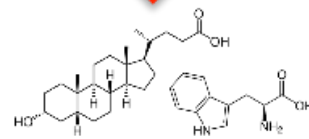
Microbiome



Environment



Metabolome

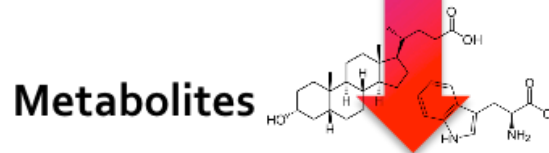
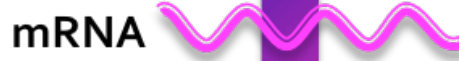


Metabolites

Genome

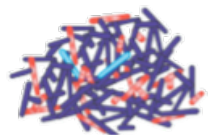
Transcriptome

Proteome



Phenotype

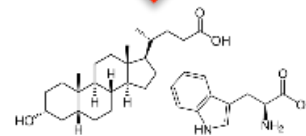
Microbiome



Environment



Metabolome



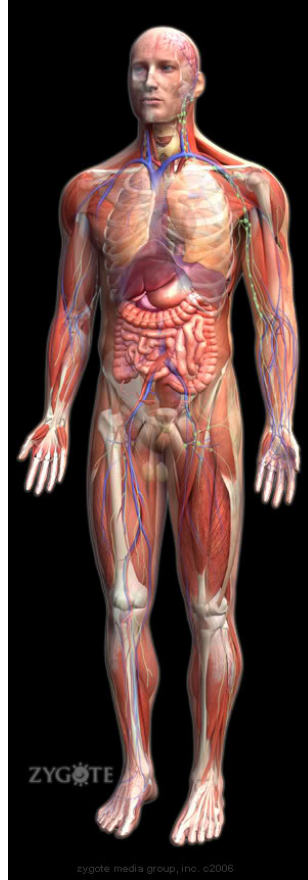
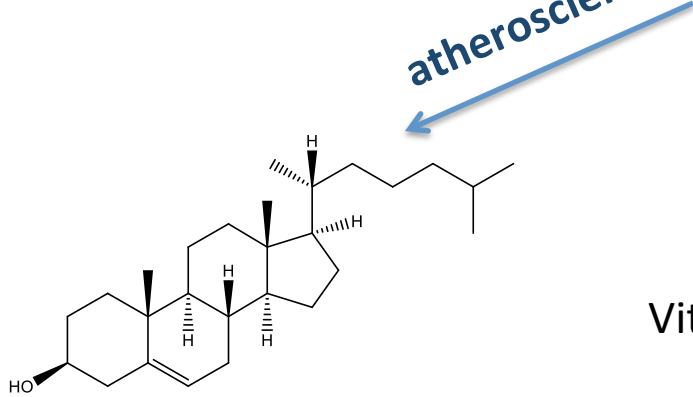
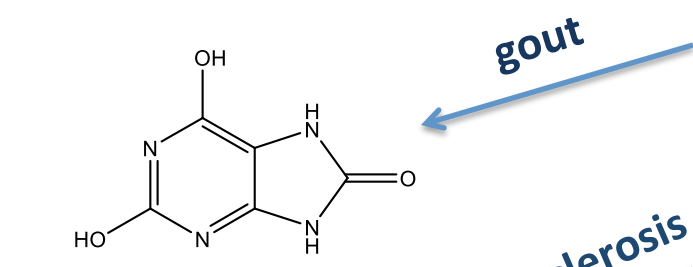
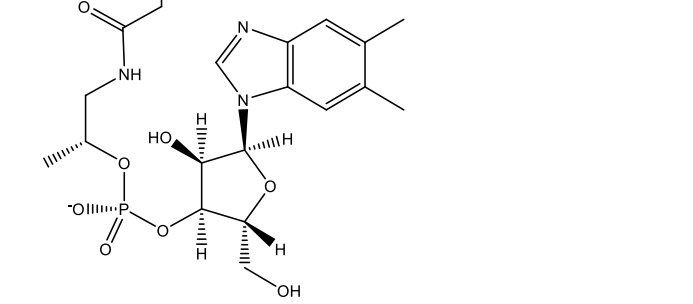
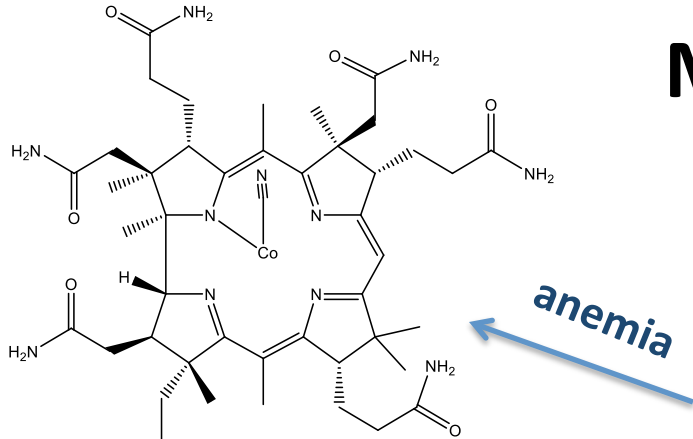
Metabolites

REGULATION

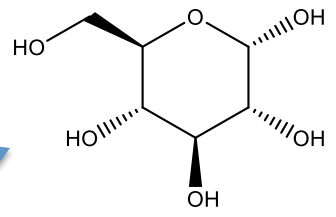




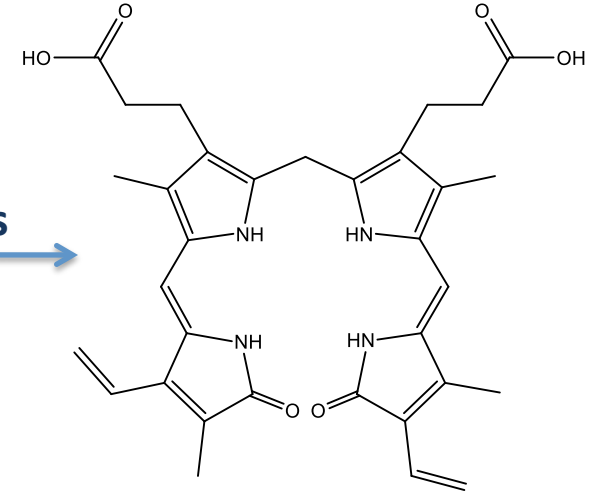
# Metabolites



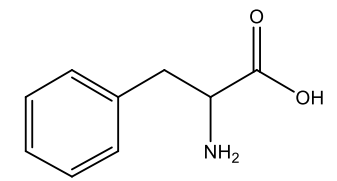
**diabetes**



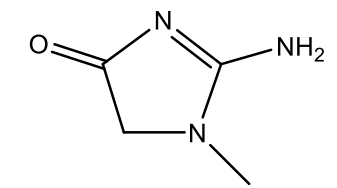
**Hepatitis**



**phenylketonuria**

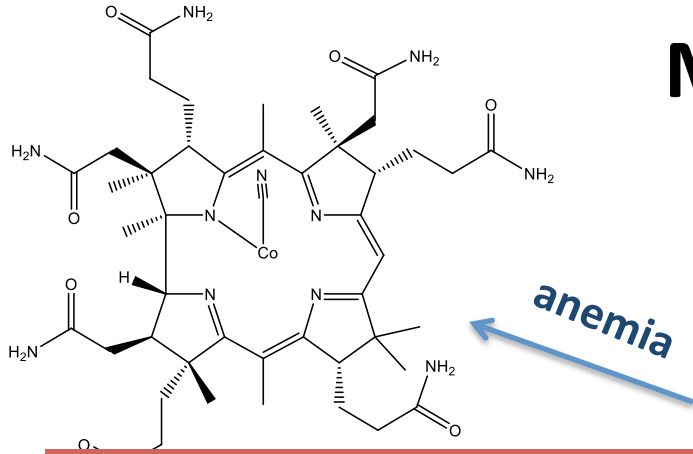


**Renal dysfunction**

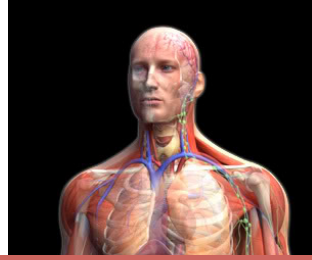


Vitamins, hormones, etc

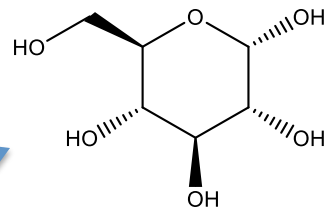
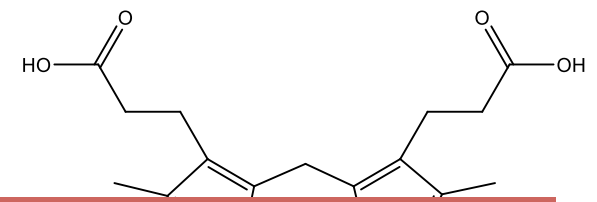
# Metabolites



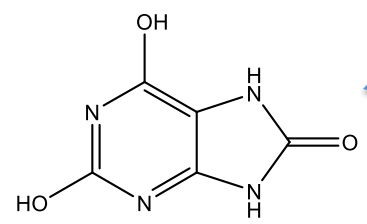
anemia



diabetes



Changes in metabolite concentrations have served as the basis to the development of more than 180 different chemical or metabolite biomarker tests that are commonly used today

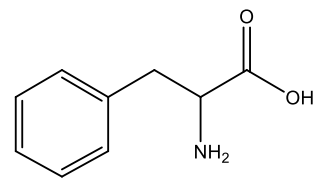


gout

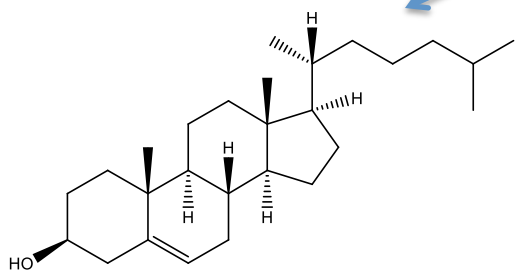
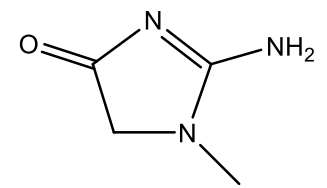
atherosclerosis



phenylketonuria



Renal dysfunction



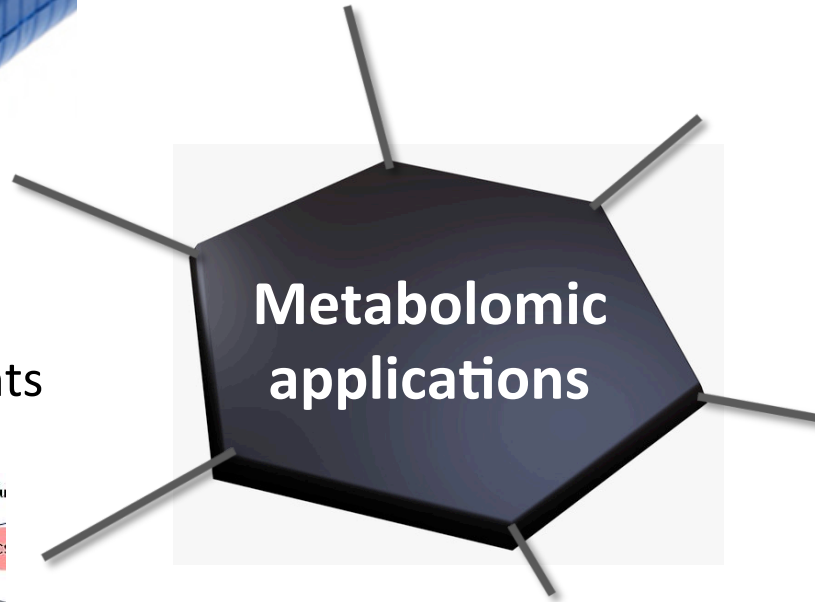
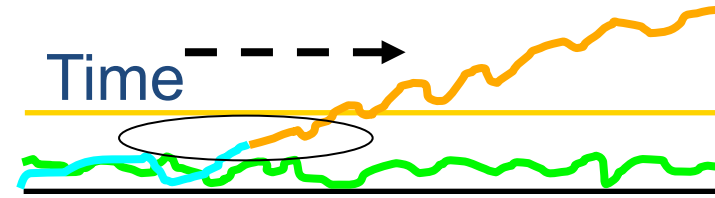
Vitamins, hormones, etc

# Drug toxicity assessment

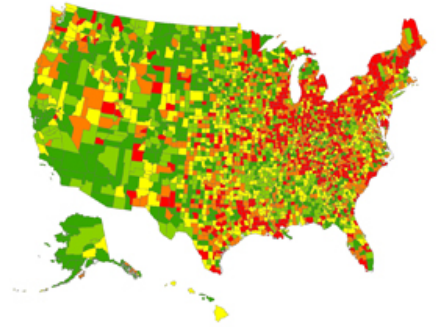
## Diagnostic markers



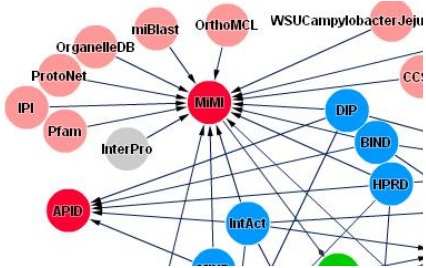
## Prognostic markers



## Epidemiological studies



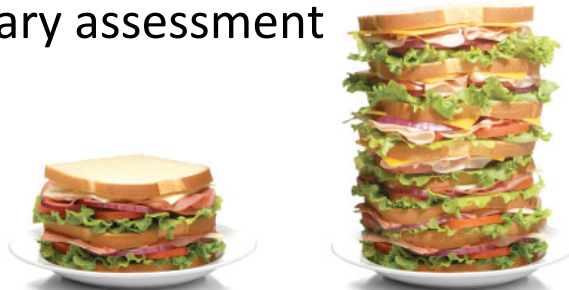
## Mechanistic insights



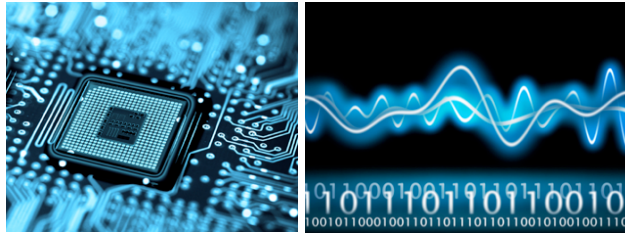
## Drug response



## Dietary assessment



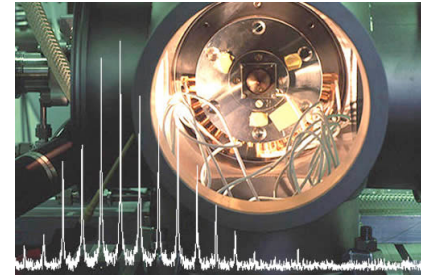
# Cross-disciplinary nature of metabolomics



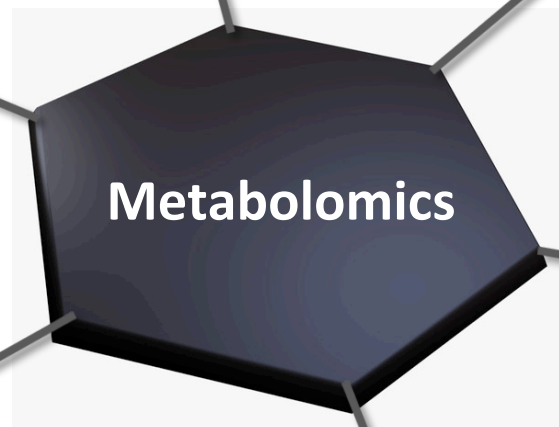
Electronic Engineering  
& Signal processing



Statistical physics

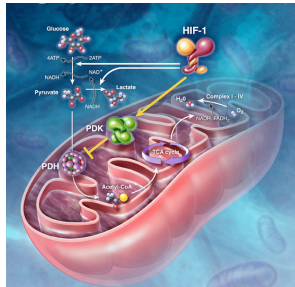


Analytical Chemistry



Metabolomics

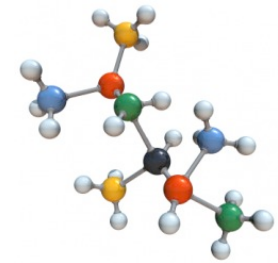
Biochemistry  
& Metabolism



Biostatistics



Organic Chemistry



# SCIENTIFIC REPORTS

OPEN

## Metabolomics reveals impaired maturation of HDL particles in adolescents with hyperinsulinaemic androgen excess

Received: 22 January 2015

Accepted: 26 May 2015

Published: 23 June 2015

Sara Samino<sup>1,3</sup>, Maria Vinaixa<sup>1,2,3</sup>, Marta Díaz<sup>1,5</sup>, Antoni Beltran<sup>1,3</sup>, Miguel A. Rodríguez<sup>1,3</sup>, Roger Mallo<sup>1,2</sup>, Mercedes Heras<sup>1,4</sup>, Anna Cabre<sup>1,4</sup>, Lorena García<sup>3</sup>, Nuria Canela<sup>3</sup>, Francis de Zegher<sup>6</sup>, Xavier Correig<sup>1,2</sup>, Lourdes Ibáñez<sup>1,5</sup> & Oscar Yanes<sup>1,2,3</sup>

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In curation



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Public



**MTBLS103: Long-term health risks in PCOS occur prematurely with serum markers of oxidative stress impacting HDL maturation through oxidation of methionine residues in apolipoprotein A1**

Authors: Sara Samino, Oscar Yanes

Submitted: 01-Aug-2014, Release date: 09-Apr-2015, Update date: 09-Apr-2015

[Share Study](#)

Study status: Public

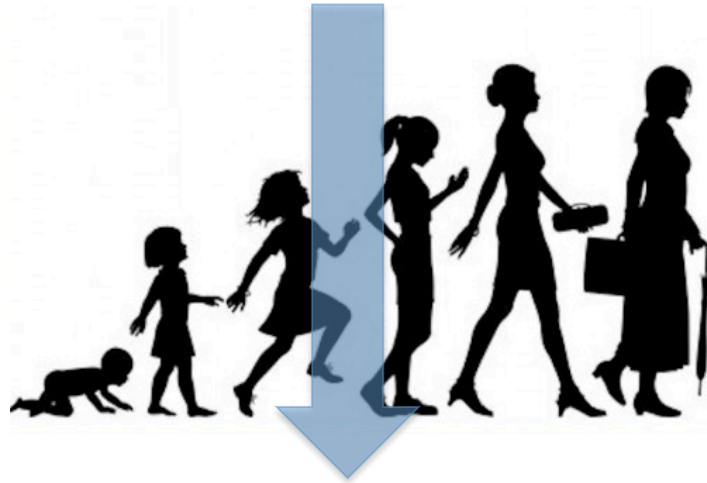
Study Description

[View Metabolites](#)

[Download Study files](#)

# Hyperinsulinemic androgen excess (HIAE) in non-obese prepubertal and pubertal girls

Long-term health risks in adulthood



- Anovulatory infertility
- PCOS phenotype

- Type 2 diabetes
- Metabolic syndrome



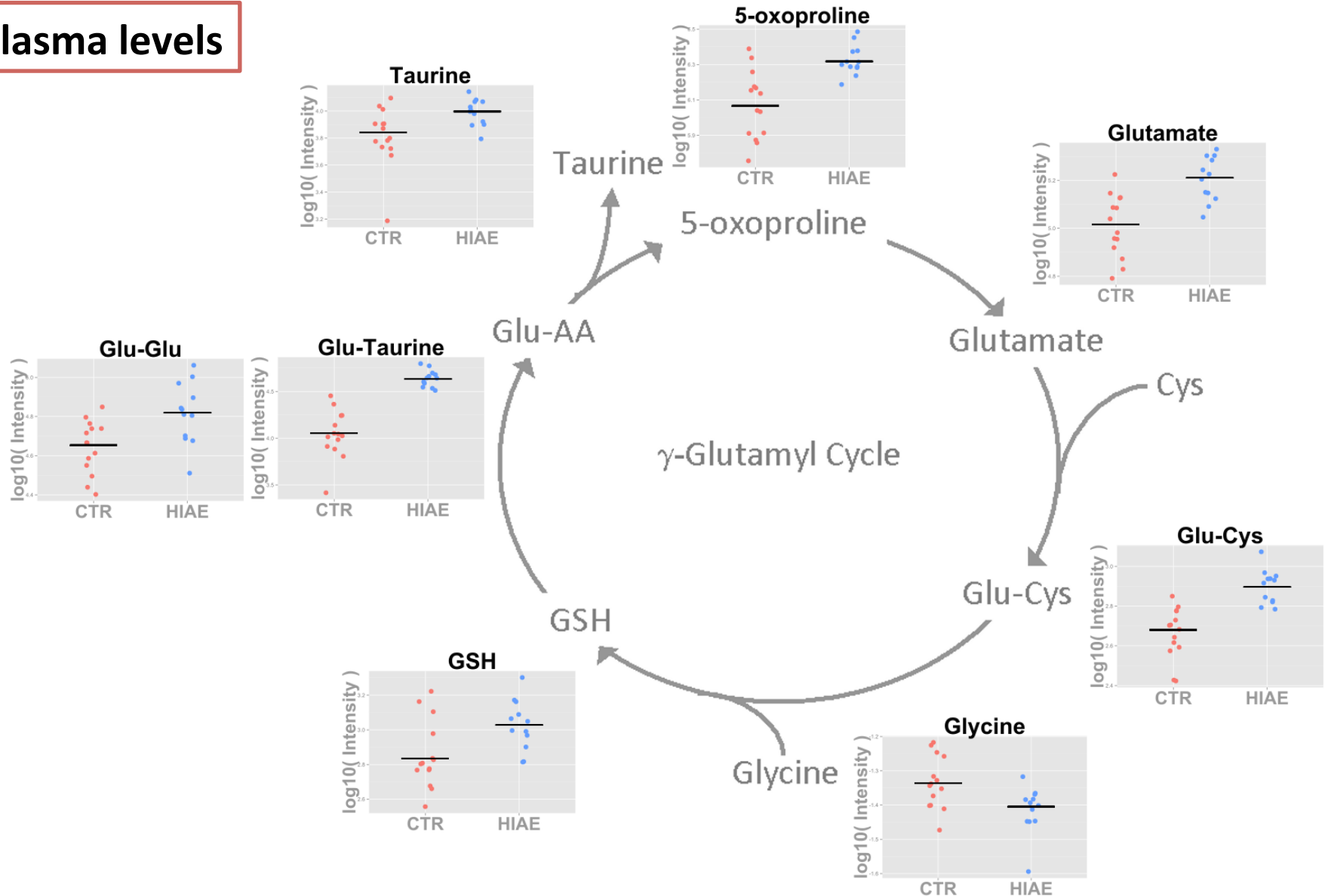
# Anthropometric and biochemical variables in HIAE patients and age- and BMI-matched controls

	CTR	HIAE	p-value
Age (yr)	17.2 ± 0.4	16.3 ± 0.4	0.15
BW SDS	0.3 ± 0.1	-0.2 ± 0.4	0.58
Wt (kg)	58.8 ± 1.8	58.2 ± 1.2	0.92
Ht (cm)	163.9 ± 1.3	160.0 ± 1.5	0.06
BMI (Kg/m <sup>2</sup> )	21.8 ± 0.6	22.8 ± 0.5	0.23
BMI SDS	0.2 ± 0.2	0.5 ± 0.2	0.16
WBC (cell/mm <sup>3</sup> )	7.3 ± 0.3	7.8 ± 0.5	0.26
Neutrophils (x1000/mm <sup>3</sup> )	4.1 ± 0.3	4.4 ± 0.5	0.63
Lymphocytes (x1000/mm <sup>3</sup> )	2.2 ± 0.1	2.5 ± 0.22	0.41
N/L (ratio)	1.9 ± 0.2	2.0 ± 0.4	0.51
AST (μL/L)	16.6 ± 0.7	16.8 ± 1.6	0.59
ALT (μL/L)	13.6 ± 1.0	13.2 ± 1.1	0.83
Glucose (mg/dL)	89.1 ± 1.5	85.4 ± 2.0	0.14
oGTT MSG (mmol/L/h)	n.d.	6.7 ± 0.3	-
(mg/dL) MSI (μU/L/h)	n.d.	45.9 ± 5.4	-
Insulin (μU/mL)	3.5 ± 0.6	10.3 ± 1.6	<b>0.01</b>
G/I ratio	32.8 ± 3.6	11.2 ± 1.9	<b>0.0004</b>
Total Cholesterol	143.9 ± 5.9	145.9 ± 6.8	0.75
HDL-cholesterol	52.6 ± 2.3	51.9 ± 3.3	0.77
LDL-cholesterol	80.5 ± 5.4	78.7 ± 4.5	0.88
Triglycerides	53.4 ± 3.6	76.8 ± 16.5	0.57
Testosterone (ng/dL)	32 ± 2.4	64.2 ± 10.2	<b>0.05</b>
DHEAS (μg/dL)	222.1 ± 27.8	280.8 ± 31.5	<b>0.03</b>
Leptin (ng/mL)	13.9 ± 2.3	20.9 ± 2.7	<b>0.05</b>
usCRP (mg/L)	0.7 ± 0.2	1.1 ± 0.2	0.14
SOD (U/mL)	6.1 ± 0.3	5.4 ± 0.2	<b>0.03</b>



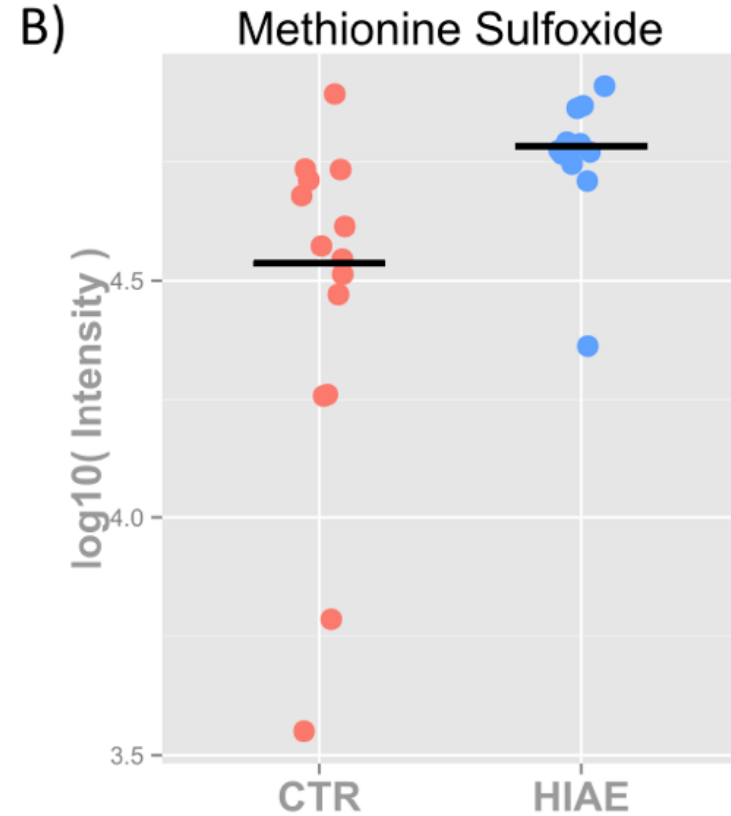
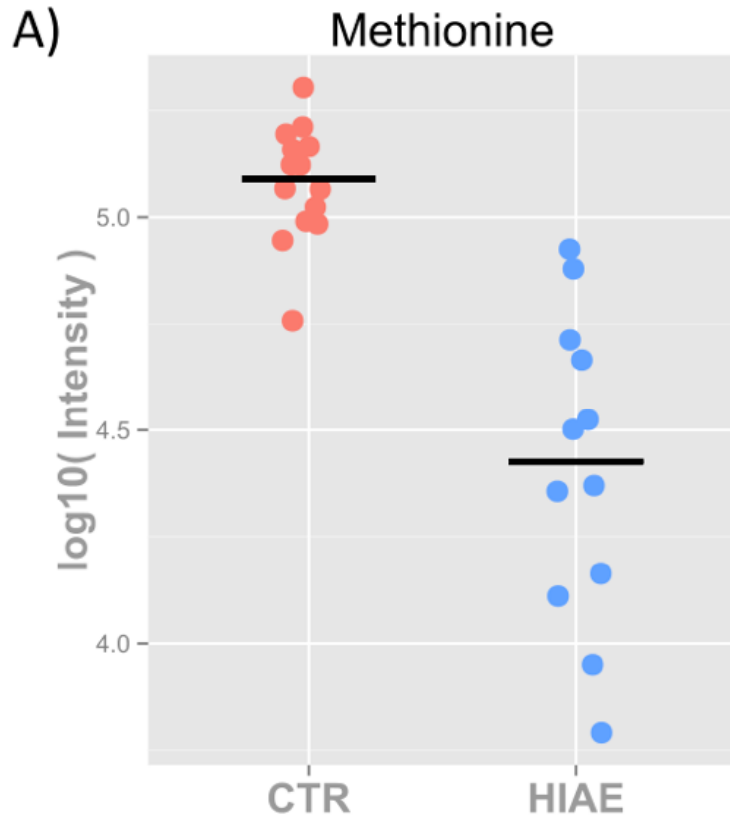
# LC-MS metabolomics reveals redox deregulation in HIAE

## Plasma levels



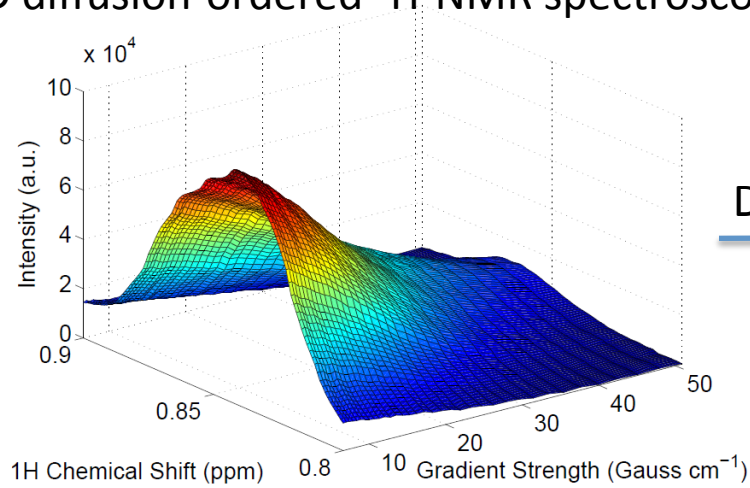
# LC-MS metabolomics reveals redox deregulation in HIAE

Plasma levels

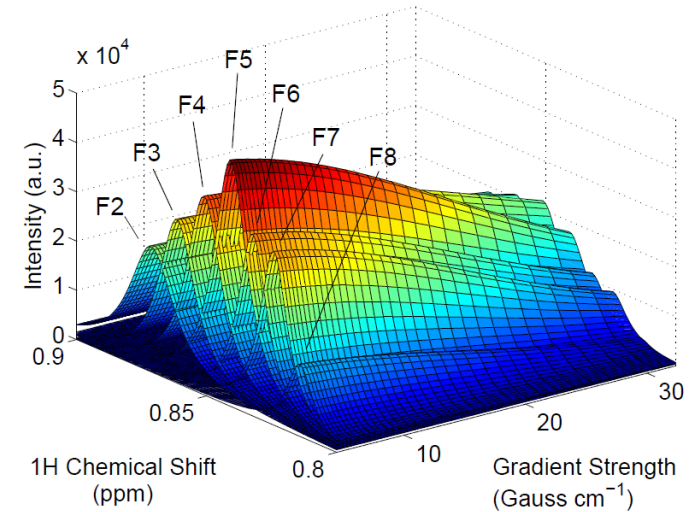


# Lipoprotein subclass characterization by NMR

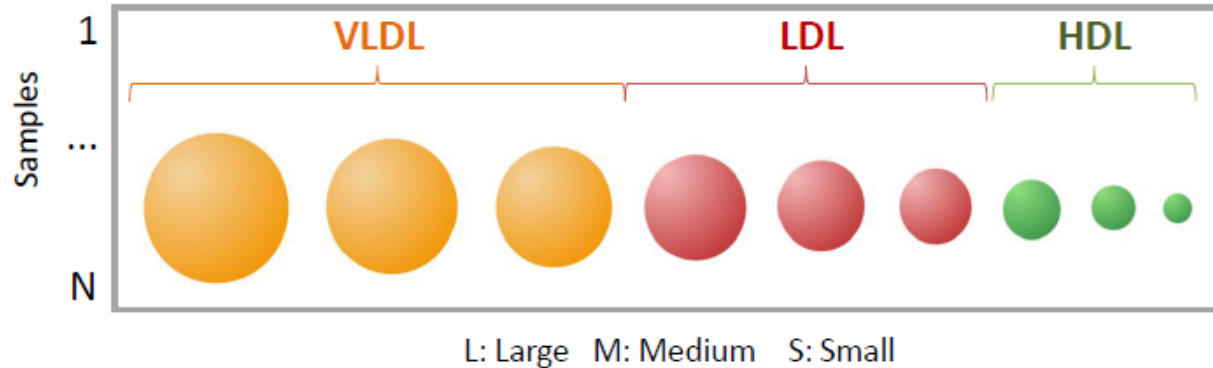
## 2D diffusion-ordered $^1\text{H}$ -NMR spectroscopy



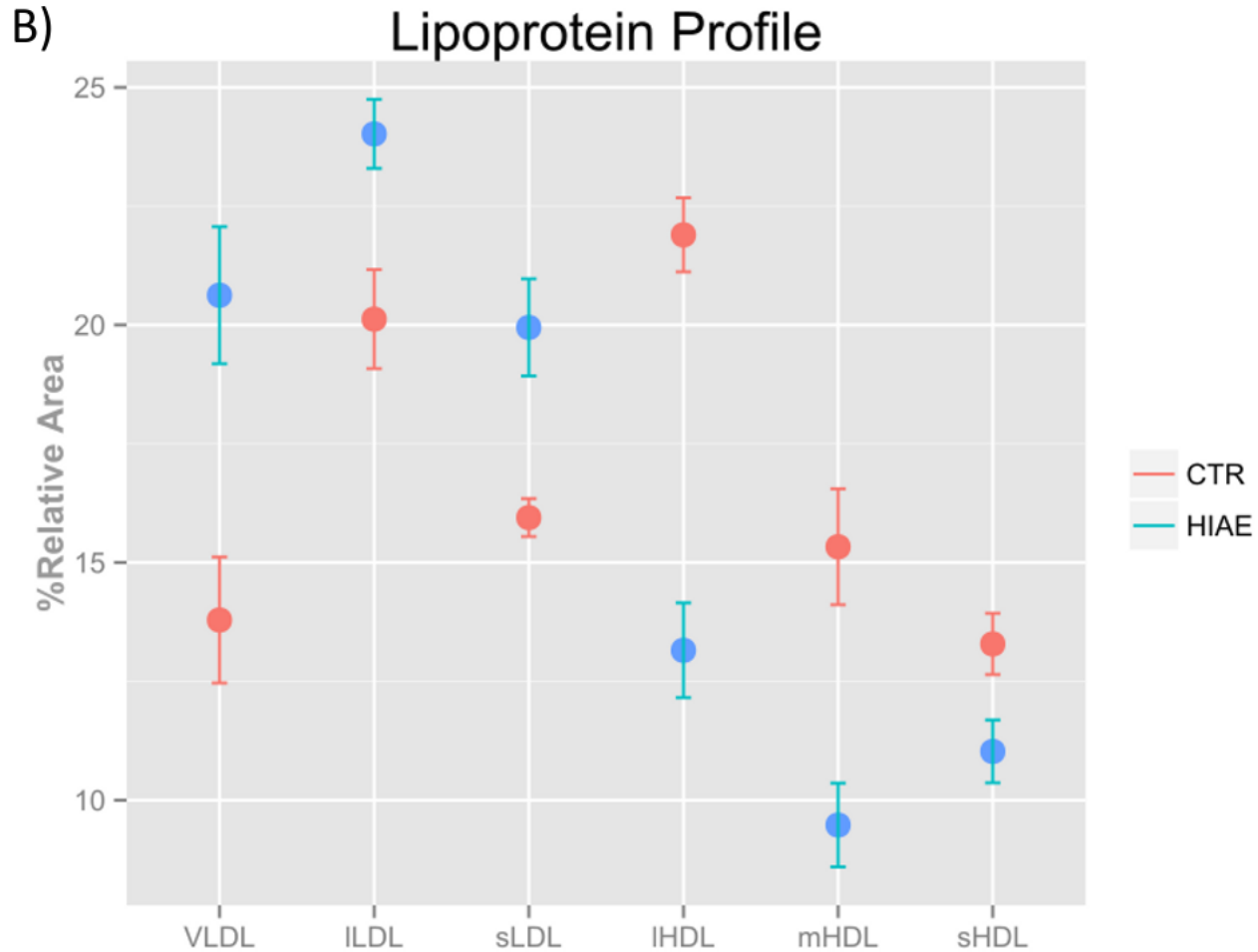
Deconvolution



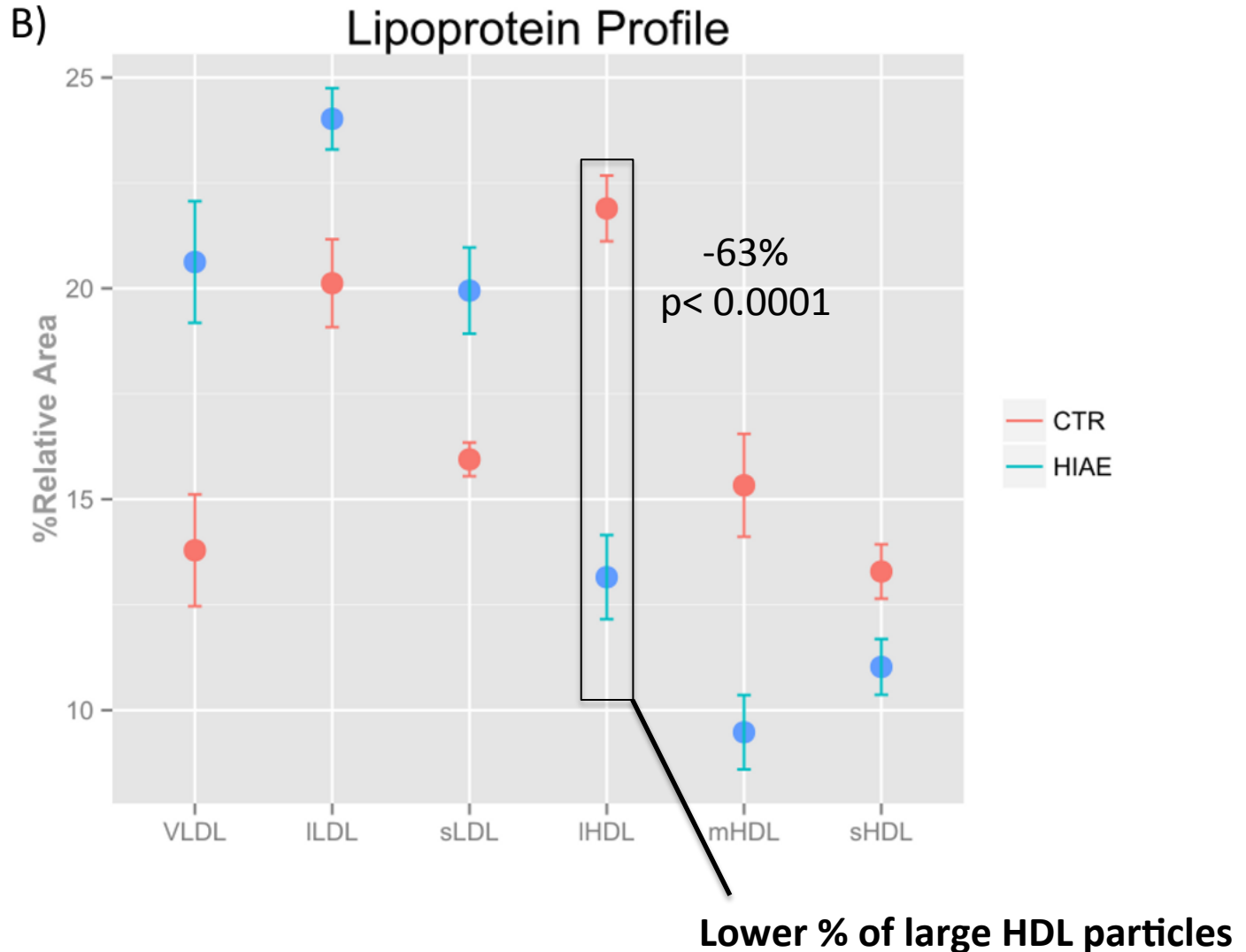
Particle number for VLDL, LDL and HDL lipoprotein classes and 9 subclasses



# Alteration of the VLDL, LDL and HDL serum profile in non-obese adolescents with HIAE



# Alteration of the VLDL, LDL and HDL serum profile in non-obese adolescents with HIAE

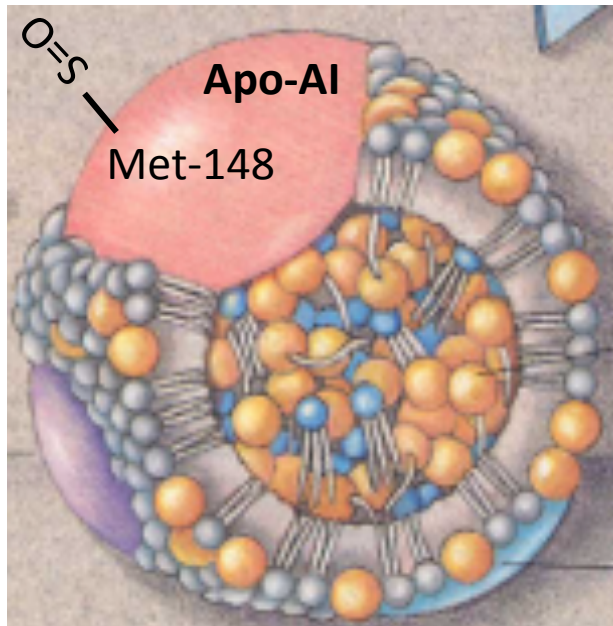


# Methionine oxidation impairs reverse cholesterol transport by apolipoprotein A-I

Baohai Shao\*, Giorgio Cavigliolo<sup>†</sup>, Nathan Brot<sup>‡</sup>, Michael N. Oda<sup>†</sup>, and Jay W. Heinecke\*<sup>§</sup>

\*Department of Medicine, University of Washington, Seattle, WA 98195; <sup>†</sup>Children's Hospital Oakland Research Institute, Oakland, CA 94609; and <sup>‡</sup>Department of Microbiology and Immunology, Weill Medical College of Cornell University, New York, NY 10021

Edited by John A. Glomset, University of Washington, Seattle, WA, and approved June 9, 2008 (received for review February 28, 2008)



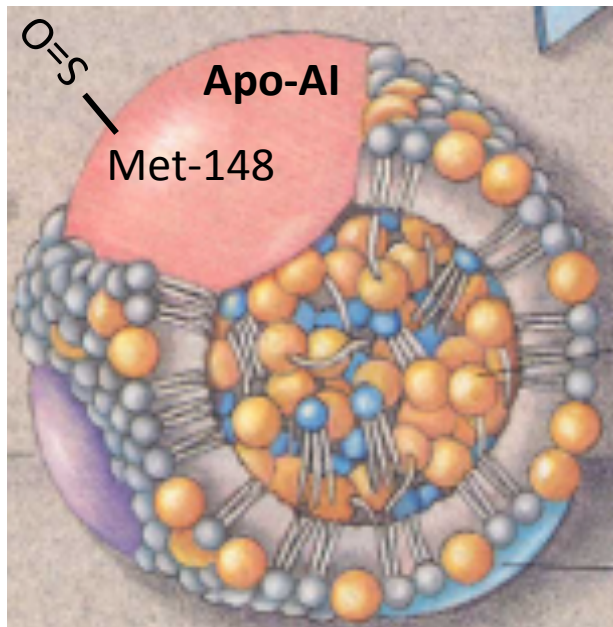
**impaired maturation of HDL particles**

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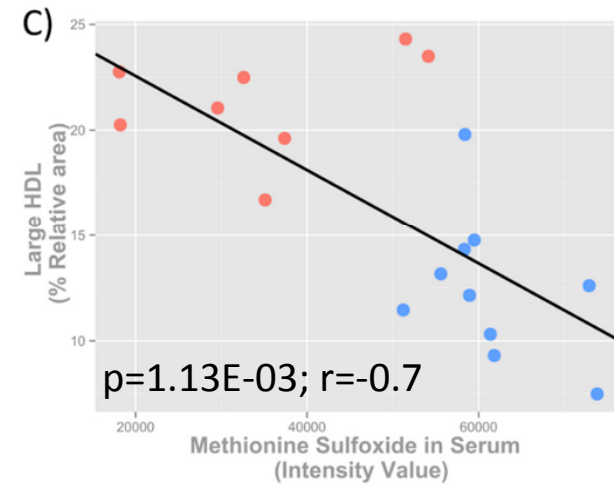
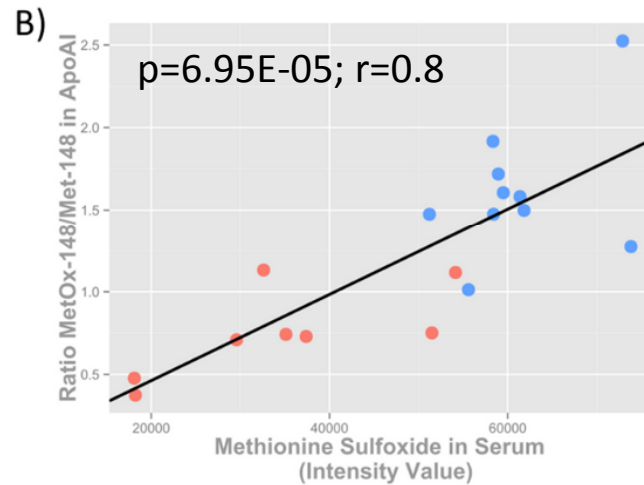
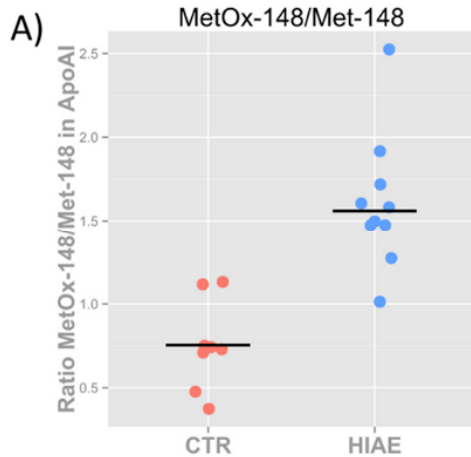
**impaired maturation of HDL particles**

## **HYPOTHESIS:**

Increased levels of free MetOx in HIAE plasma may reflect greater oxidation of methionine residues in Apo-AI of HDL particles



# Quantitative analysis of the MetOx-148/Met-148 ratio in apo-A1 by MALDI-TOF MS



**Levels of free methionine sulfoxide in serum reflect HDL oxidation, and indirectly, impaired maturation of HDL particles**

 **Low sugar consumption is associated with increasing HDL levels in females during adolescence**

J Am Heart Assoc. 2014 Feb 26;3(1):e000615. doi: 10.1161/JAHA.113.000615.

**Consumption of less than 10% of total energy from added sugars is associated with increasing HDL in females during adolescence: a longitudinal analysis.**

Lee AK<sup>1</sup>, Binongo JN, Chowdhury R, Stein AD, Gazmararian JA, Vos MB, Welsh JA.

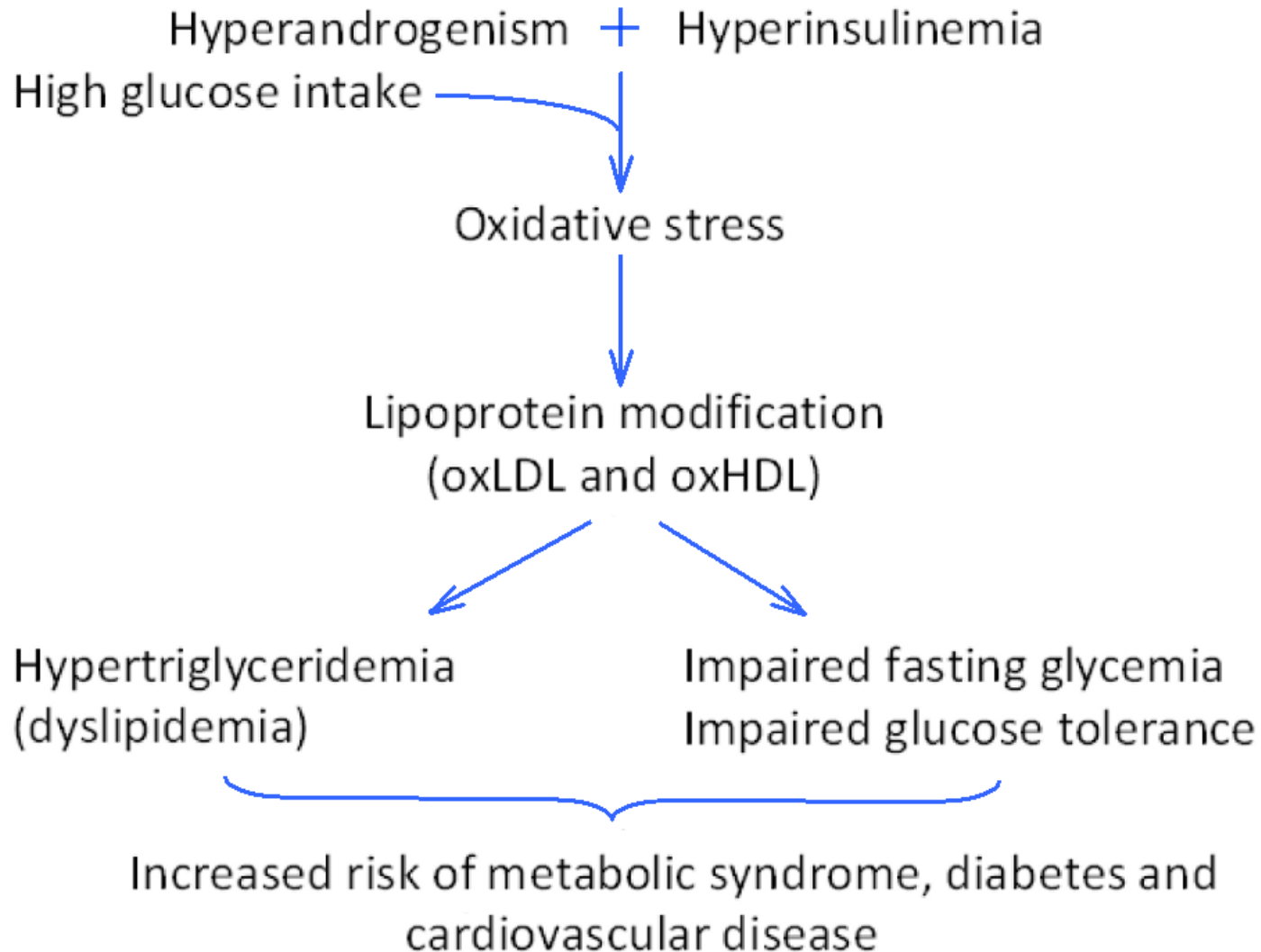
 **Excessive sugar intake in combination with hyperandrogenism causes oxidative stress**

J Clin Endocrinol Metab. 2012 Aug;97(8):2836-43. doi: 10.1210/jc.2012-1259. Epub 2012 May 8.

**Hyperandrogenism sensitizes leukocytes to hyperglycemia to promote oxidative stress in lean reproductive-age women.**

González F<sup>1</sup>, Nair KS, Daniels JK, Basal E, Schimke JM, Blair HE.

# Proposed mechanism to explain the long-term health risks of hyperinsulinaemic androgen excess

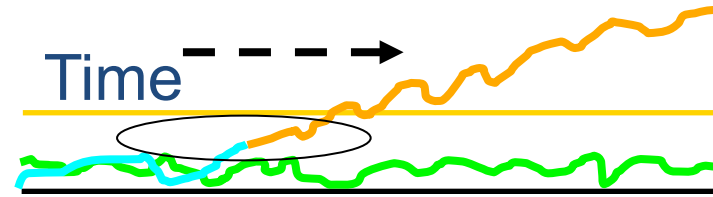


# Drug toxicity assessment

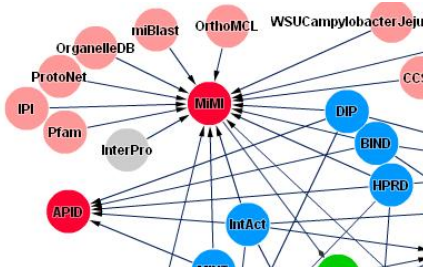
## Diagnostic markers



## Prognostic markers

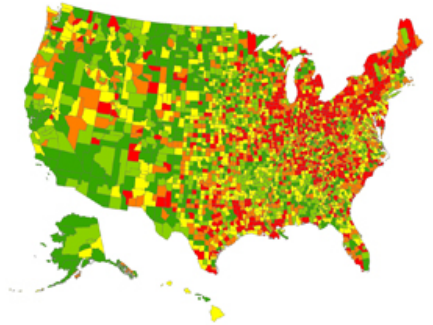


## Mechanistic insights

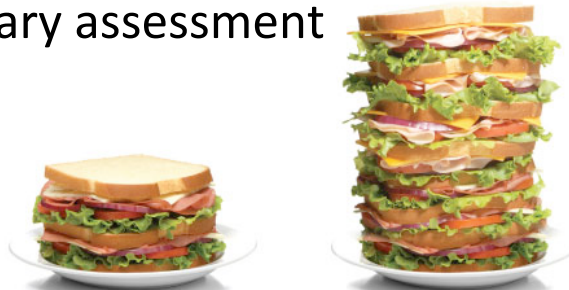


# Metabolomic applications

## Epidemiological studies



## Dietary assessment



## Drug response



# Effects of Oral Contraceptives in Adolescents with PCOS

- Reduction of hirsutism, acne & seborrhea
- Anovulation & pseudo-menses
- Pharmacological sex hormone binding globulin (SHBG) elevation
- More adipose: more fat mass & less lean mass

# Non-Obese Adolescents

## Metformin & AR-Blockade & Low-Dose Pioglitazone

have many normalizing effects, including on:

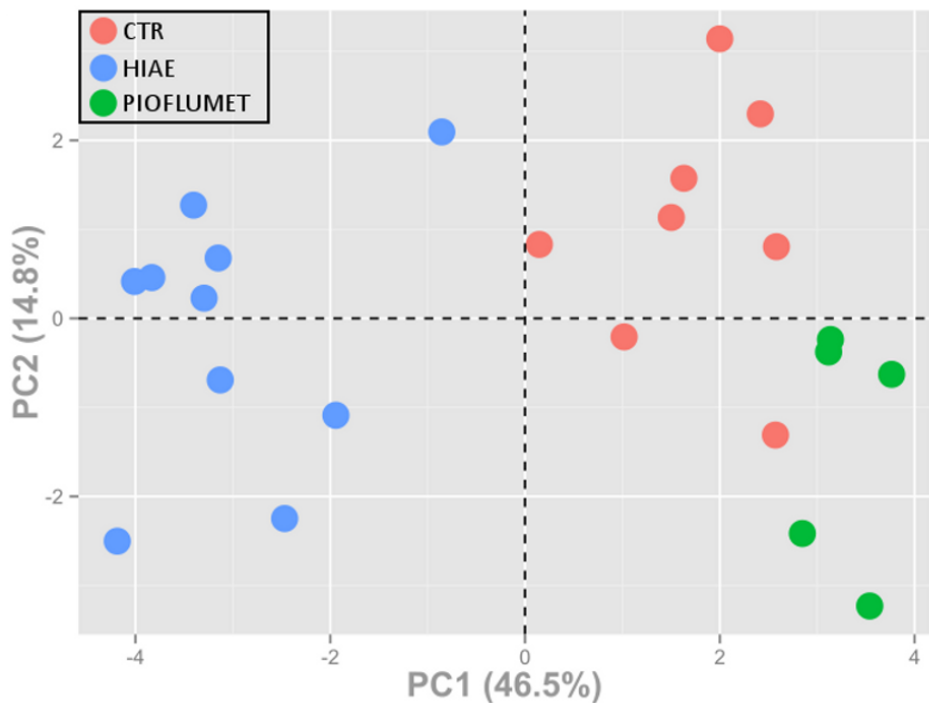
- Hirsutism (lower F-G scores)
- Menstrual cycle (more regular)
- Insulinemia (lower)
- Lipidemia (less atherogenic) & **IMT (lower)**
- Markers of low-grade inflammation (CRP)
- Body composition: less Fat, **more Lean Mass**
- **Adiponectin (higher)**

*Ibáñez, JCEM 2002-13*

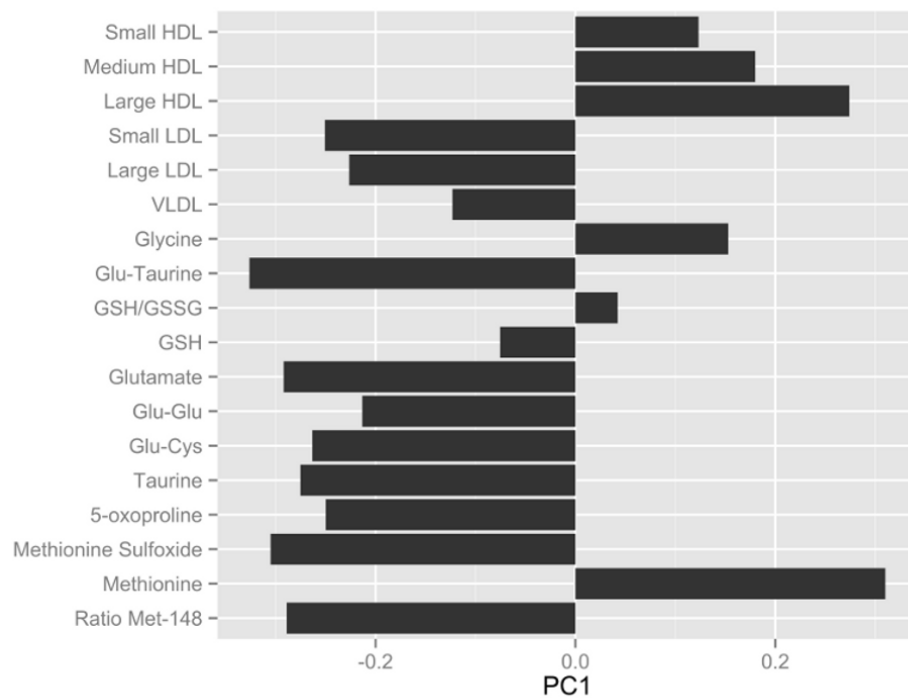
*Ganie, JCEM 2013*

# Metabolic changes after 18 months of low dose PioFluMet polytherapy

## Principal Component Analysis (PCA)

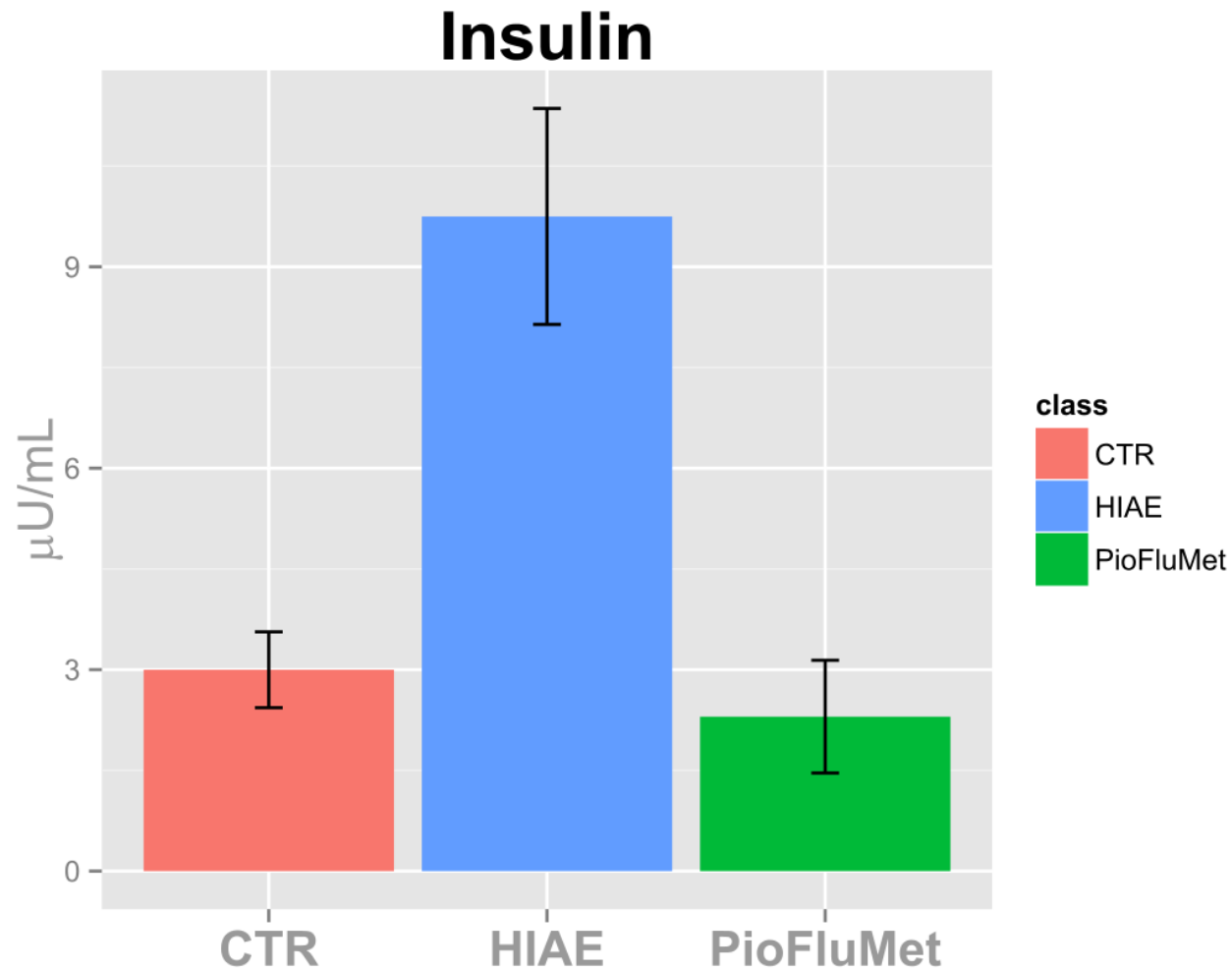


## Loading bar plot

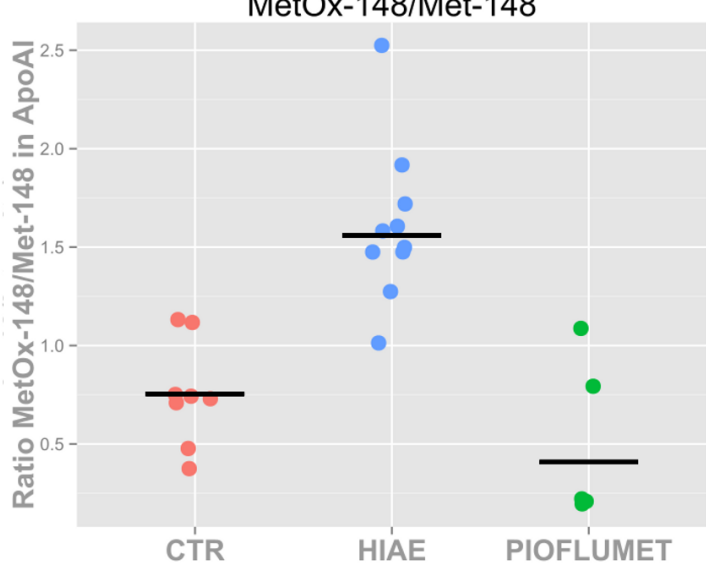
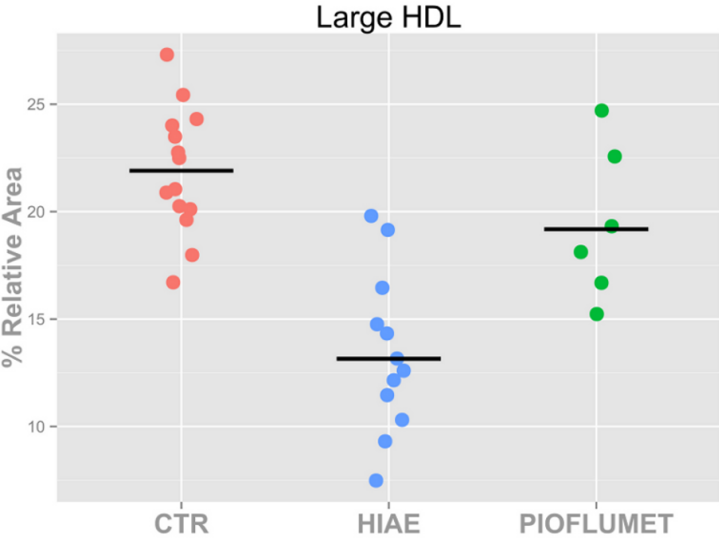
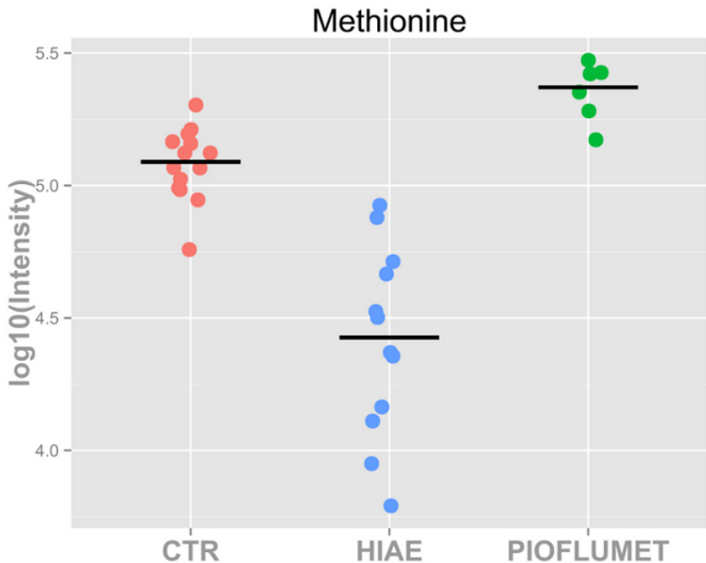
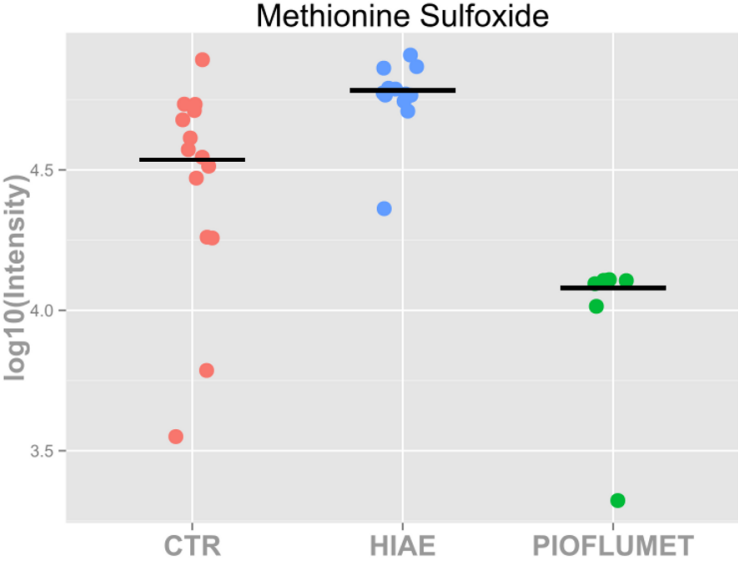








# Metabolic changes after 18 months of low dose PioFluMet polytherapy



# Metabolic changes after 18 months of PioFluMet polytherapy



# Precise vs. Accurate Medicine

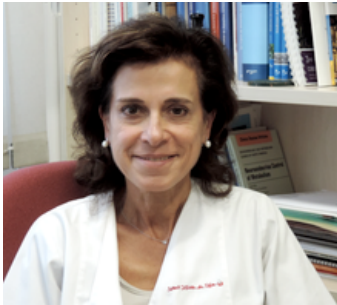
		Precise	
		Yes	No
Accurate	Yes		
	No		



## Monitor Me - BBC Documentary - BBC Horion

<https://www.youtube.com/watch?v=V5yLlp8AK9U>

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