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SCHOOL OF MEDICINE PHYSICAL MEDICINE AND REHABILITATION

Use of Metabolomics Analysis in Clinical Trials to Capture the Exposome

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Take home message: there is still a lot to be developed!

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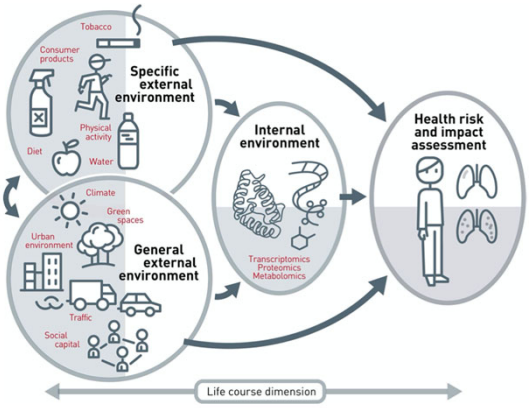
Exposome

- The totality of human environmental (non-genetic) exposures from conception onwards, complementing the genome.



Wild CP, Cancer Epidemiol Biomarkers Prev. 2005 Aug;14(8):1847-50

Vrijheid M. Environ Health Perspect, Thorax 2014;69:876-878

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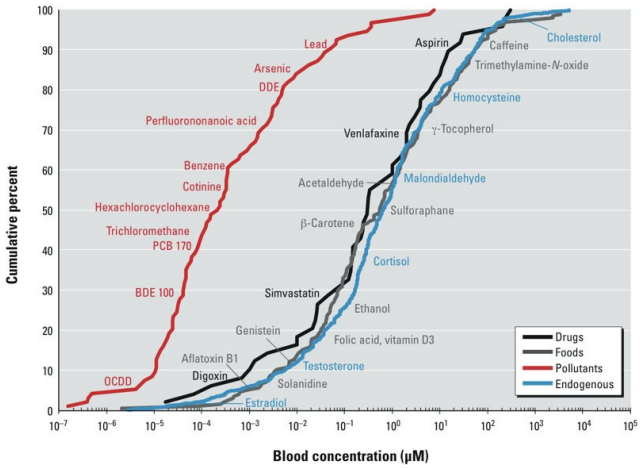
Cumulative distribution of chemical concentrations in blood



Rappaport, Environ Health Perspect. 2014

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Global Death Attributed to Exposure-risk Factors for Chronic Diseases

Risk factor	Attributed deaths	Percent of global deaths
Tobacco smoking	5,695,349	11.28
Indoor smoke	3,478,773	6.89
Ambient particulate pollution	3,223,540	6.38
Diet high in sodium	3,104,308	6.15
Alcohol use	2,735,511	5.42
Diet low in seafood omega-3 fatty acids	1,389,896	2.75
Lead exposure	674,038	1.33
Second-hand smoke	601,938	1.19
Diet low in polyunsaturated fatty acids	533,603	1.06
Diet high in trans fatty acids	515,260	1.02
Occupational chemicals	373,738	0.74
Drug use	157,805	0.31
Ambient ozone pollution	152,434	0.30
Diet low in calcium	125,594	0.25
Vitamin A deficiency	119,762	0.24
Iron deficiency	119,608	0.24
Residential radon	98,992	0.20
Zinc deficiency	97,330	0.19
TOTAL	**23,197,479**	**45.9**

World Health Organization estimates of exposures affecting global deaths in 2010

Rappaport SM. PLoS One. 2016 Apr 22;11(4):e0154387.

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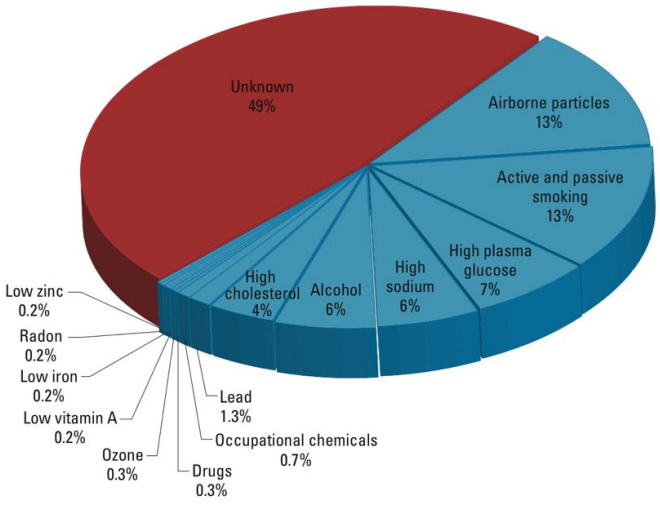
Risk factors for exposures that contribute to chronic-disease mortality.



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Exposome in Clinical Trials with Free-living Participants

- Are participants exposed to additional chemicals that confound the intervention effect?

-Pesticides and antibiotics in produce

-Chemicals in makeup and skincare

-Dyes in clothing items

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Exposome in Clinical Trials with Free-living Participants

- Are participants taking medications as they reported?
- Varied drug metabolism among patients
- Are the medications interfering with the intervention?

Drug efficacy and safety

Nutrition-related

-Appetite

-GI issues

-Metabolism

Self-reports are not always accurate and medical records are not always accessible

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Our exploratory analysis

Goal

Explore the feasibility of using untargeted metabolomics analysis to identify the medications, food-related components, and environmental chemicals participants are exposed to.

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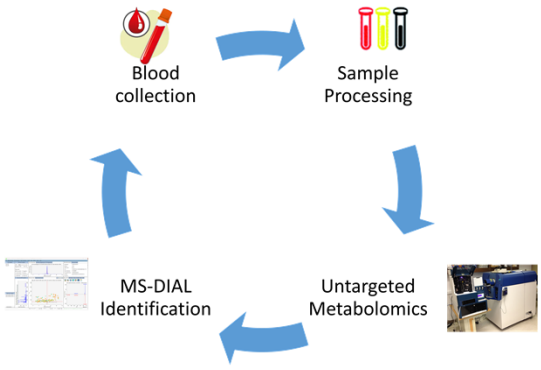
Methods

54 serum samples from participants with spinal cord Injury in a dietary interventional study



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Methods

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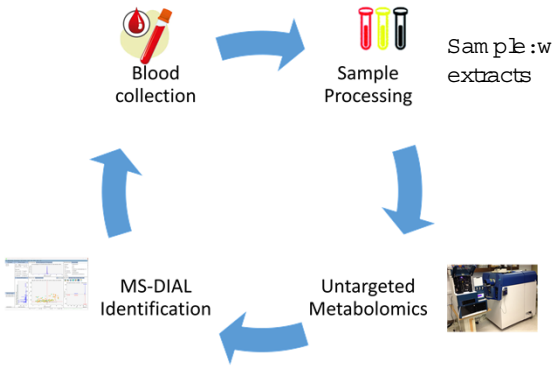

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Methods

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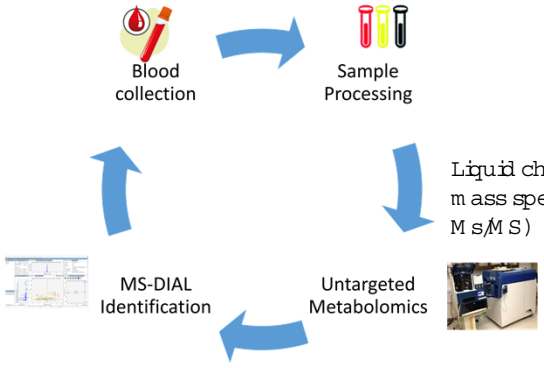

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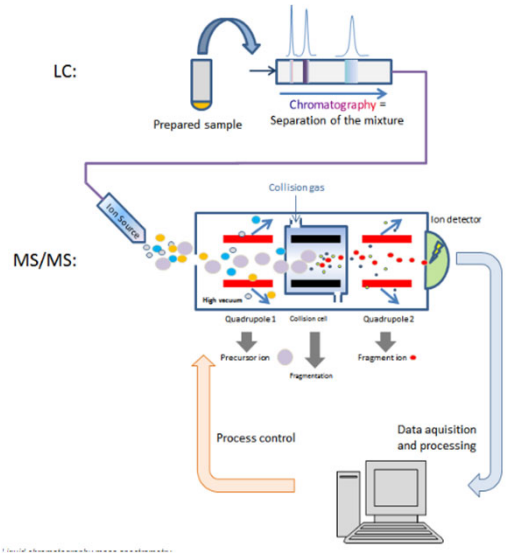
LC-MS/MS



- LC process separates ions by retention time
- MS/MS process
  - –The first MS filters for the precursor ions
  - –Fragmentation of precursors by high energy
  - –The 2nd MS: filter fragmented ions
- The fragmentation pattern can help ID the precursor

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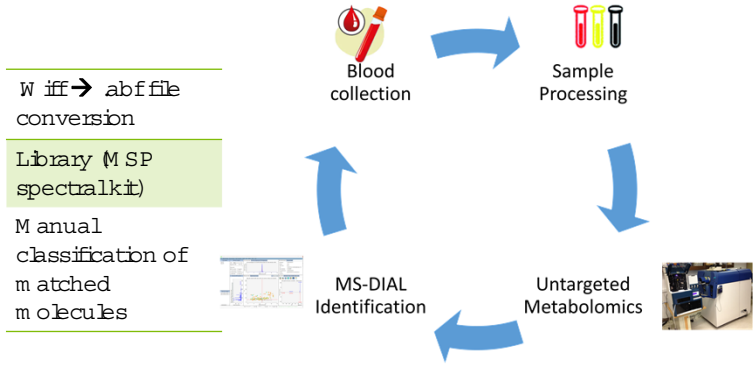
MS-DIAL

54 serum samples from participants with spinal cord Injury in a dietary interventional study



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Results: Overview of Detected Ion Features

Total Ion Feature Matched	423
Drugs and metabolites/excipients	108
Food/food additives	71
Plant compounds in dietary supplements	25
Physiological intermediates	167
Chemicals (flame retardants, insecticides, cosmetics and solvents)	19
Others	33

Continuously updated

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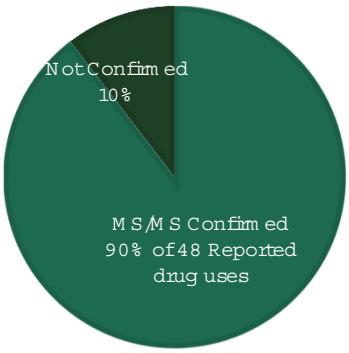
Results: MS/MS confirmation vs self-reported medication use



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Conclusion and Discussions

- Untargeted metabolomics analysis as an option/supplementary tool to explore the Exposome (including participant drug use/abuse)

BUT

- The list of drugs considered "matched" are limited by a peak intensity threshold and library/reference availability
- Chemical identification process is not automated and time-consuming
- Only extracted water-soluble molecules can be detected; separate sample preparation/analyses needed.
- Serum sample may only represent a snapshot of exposure

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