MetaMob project

Identify metabolic pathways associated with frailty in a cohort of elderly people

Nutrition

Mobility

Healthy ageing

Prediction

Metabolomics

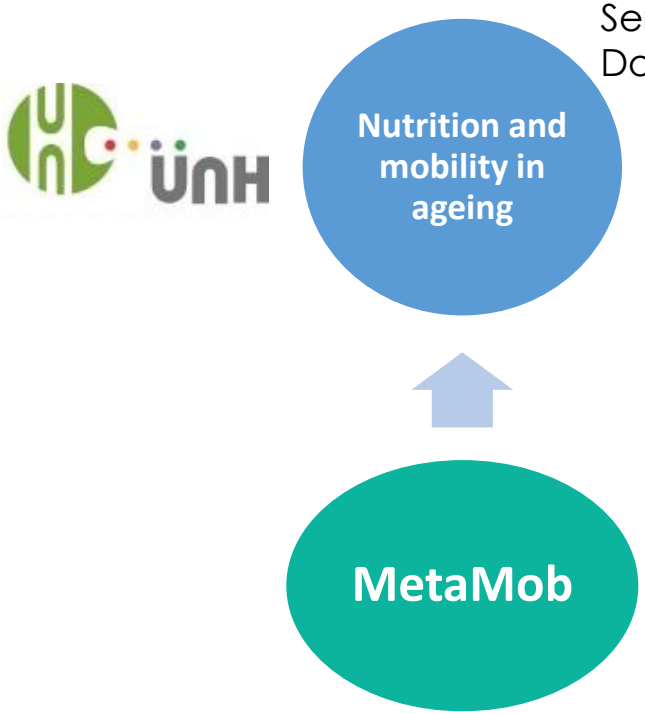
A multidisciplinary consortium

MetaMob

FUNDING

A multidisciplinary consortium

Sergio Polakof
Dominique Dardevet



FUNDING

CAP 20-25 I-SITE Clermont
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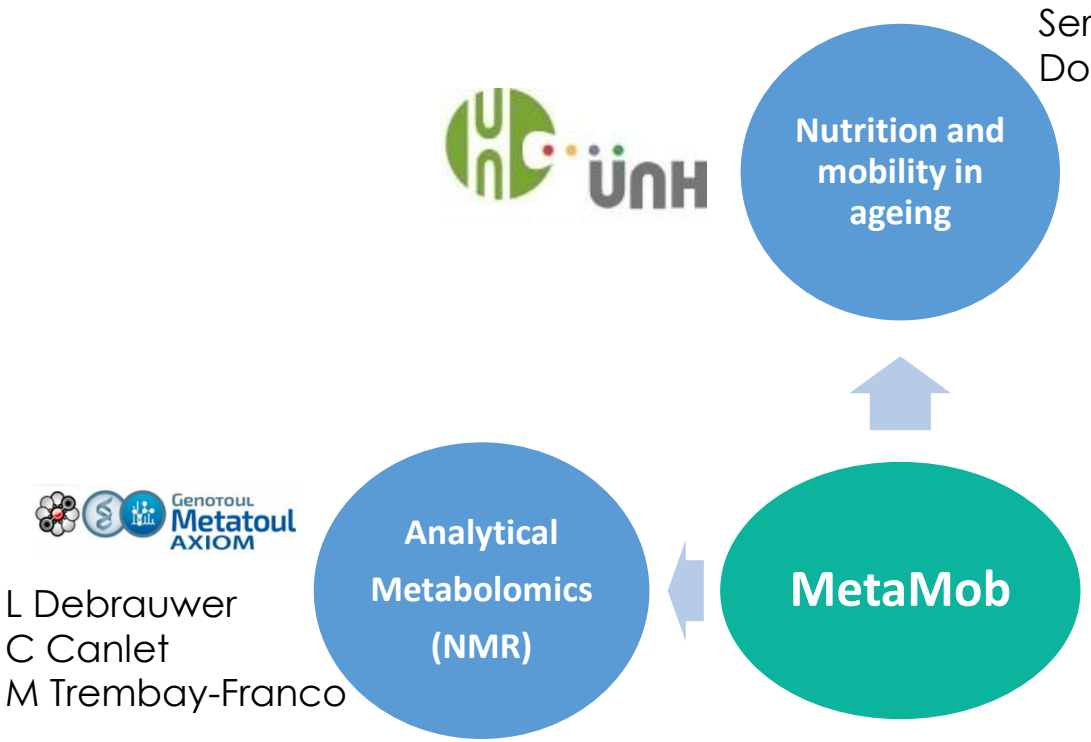
Home > Research > Scientific Challenges > Personalised mobility as a key factor in health

Challenge 3: Personalised mobility as a key factor in health

...

Objective: Analyze the mechanisms driving or impeding individual mobility and propose optimization strategies

A multidisciplinary consortium



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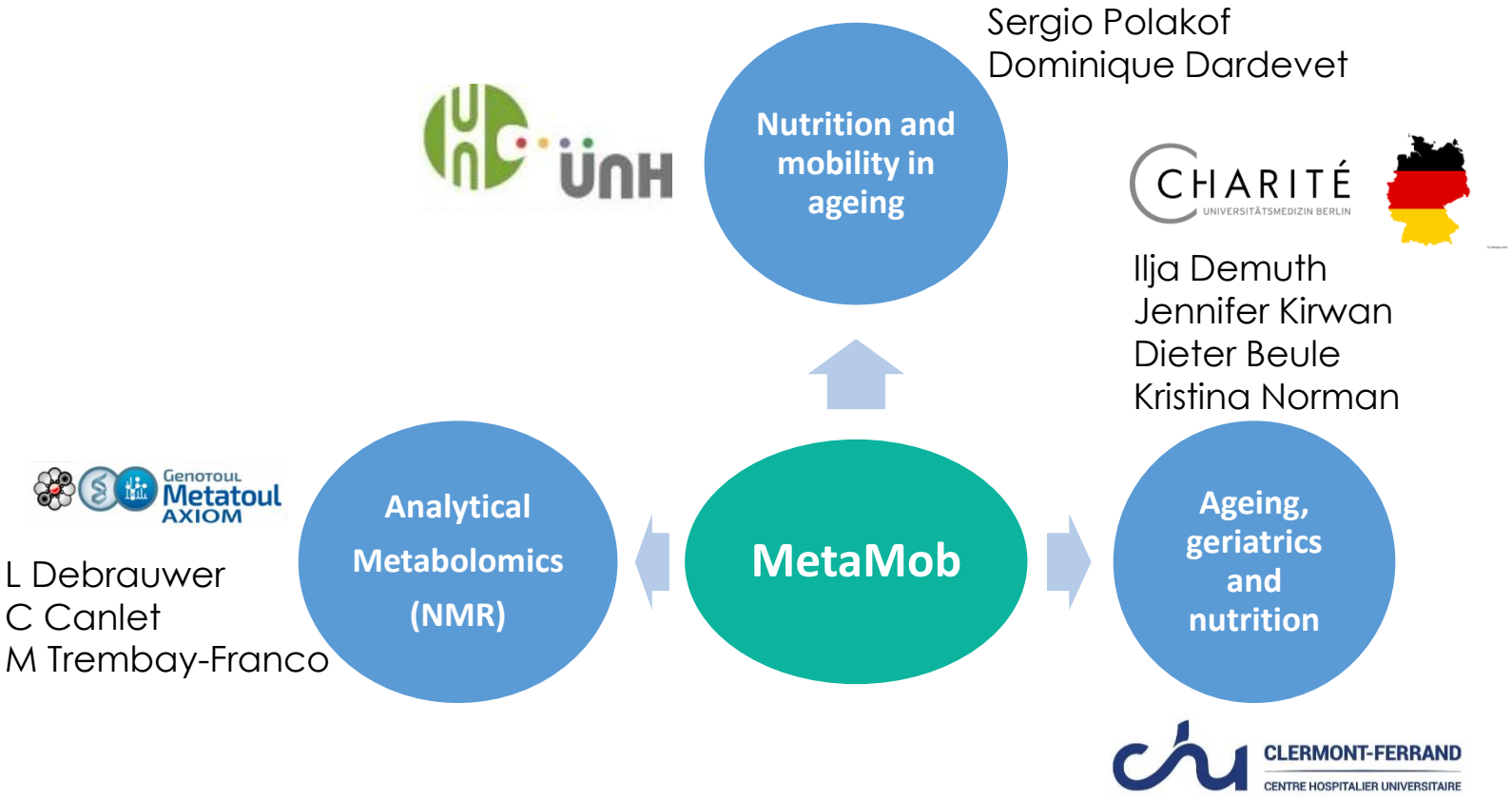

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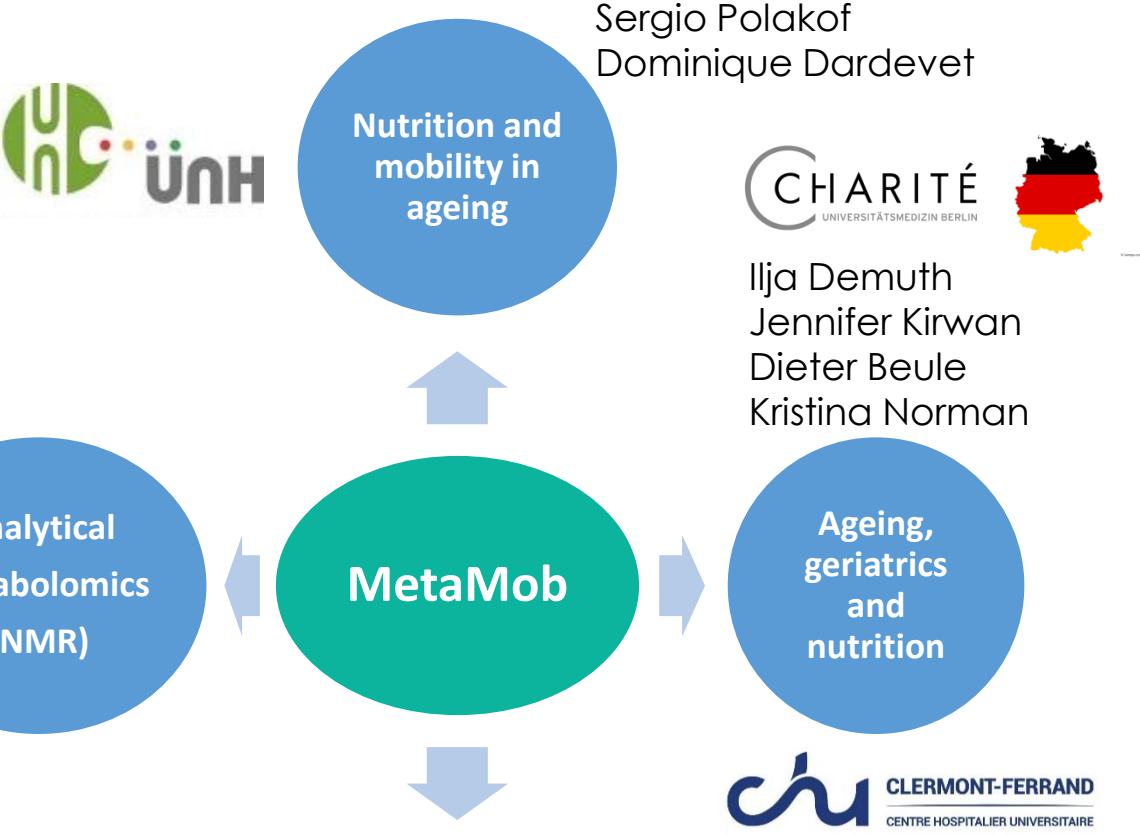

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...

Objective: Analyze the mechanisms driving or impeding individual mobility and propose optimization strategies

Why study frailty?

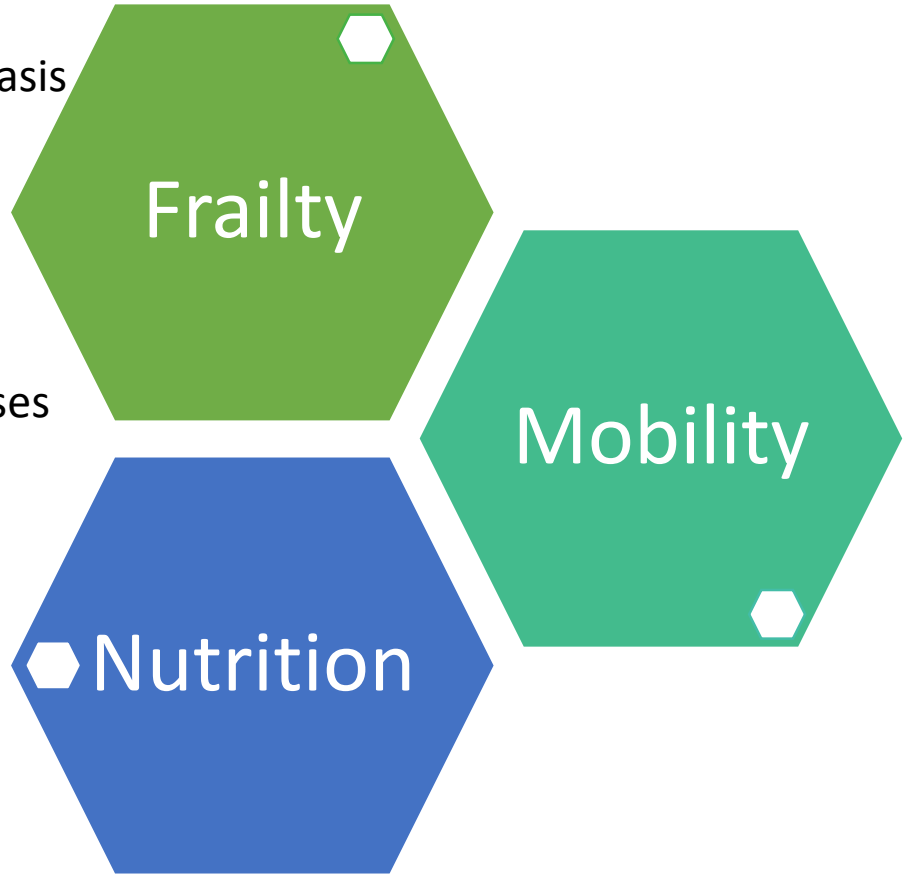
Complex clinical state
- Loss of physiological homeostasis
- Loss of ability to adapt to the environment

↓

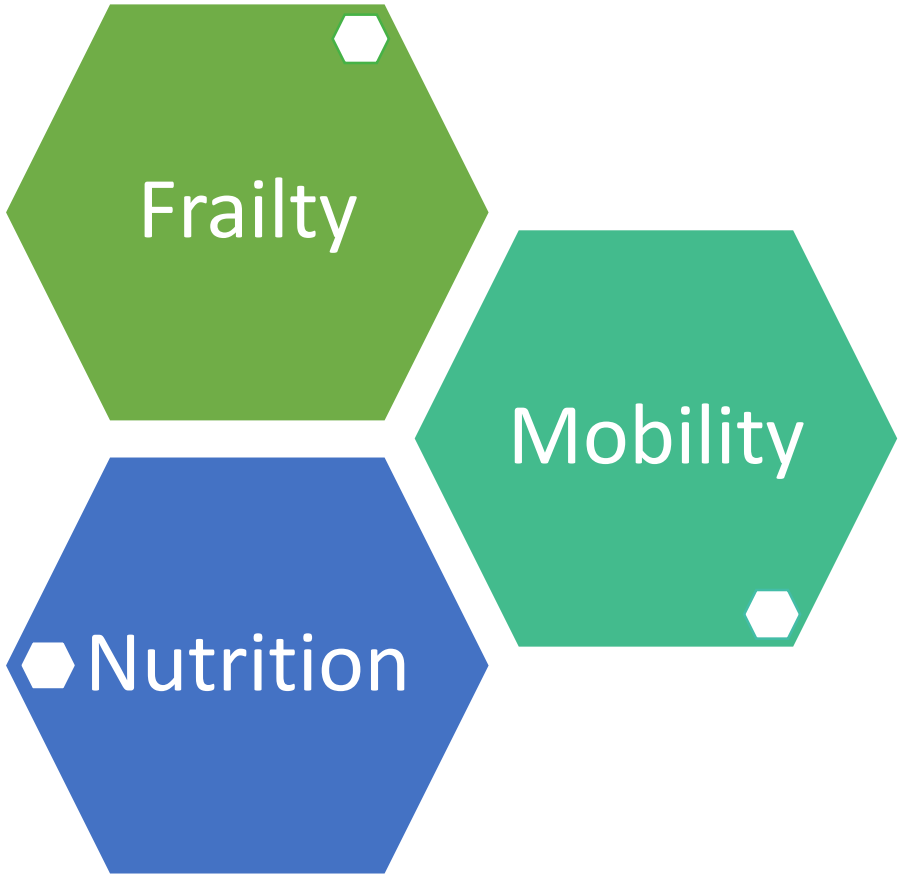
Risk of adverse outcomes increases

↓

Identify fragility levels + prevention



Why study frailty?



Frailty diagnostic?

- functional and nutritional status
- cognition
- Emotional state,
- comorbidities
- polypharmacy
- socio-economic status
- Other geriatic syndromes gériatriques (sensory impairment, urinary incontinence, ...)

Identify metabolic pathways associated with frailty in a cohort of elderly people.

1

2

Where are the data to do this project?

Open access Cohort profile

BMJ Open **Cohort profile: follow-up of a Berlin Aging Study II (BASE-II) subsample as part of the GendAge study** Ilja Demuth et al. (2021)

At baseline:

At the end of follow-up:

901 old people

1

2

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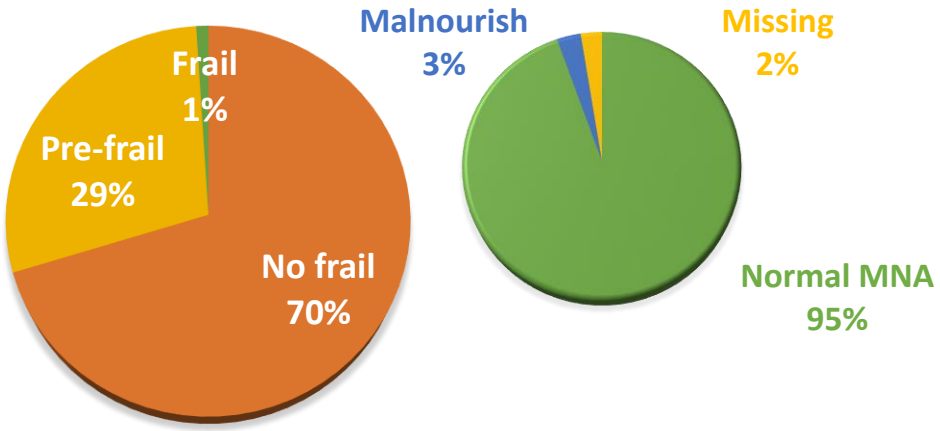
At baseline:

At the end of follow-up:

Clinical phenotypic data
+ NMR metabolomic serums

901 old people



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1

2

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At baseline:

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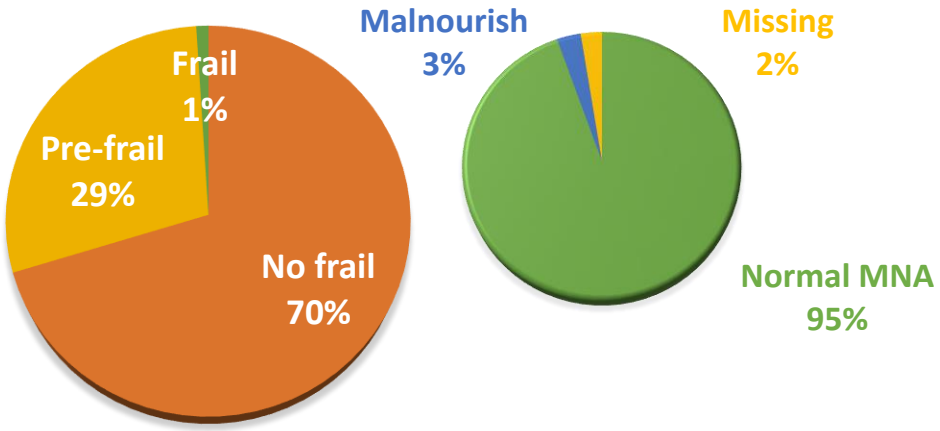
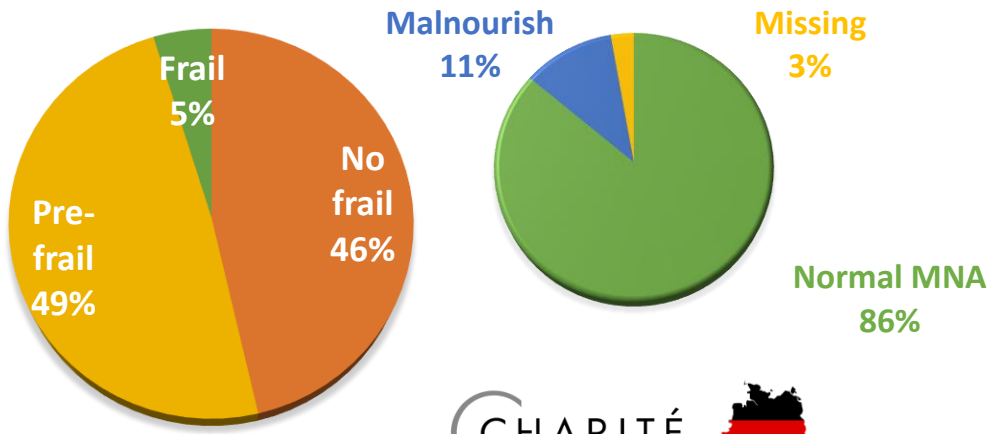
Clinical phenotypic data
+ NMR metabolomic serums

Clinical phenotypic data

901 old people

7,4 years ± 1,5 years





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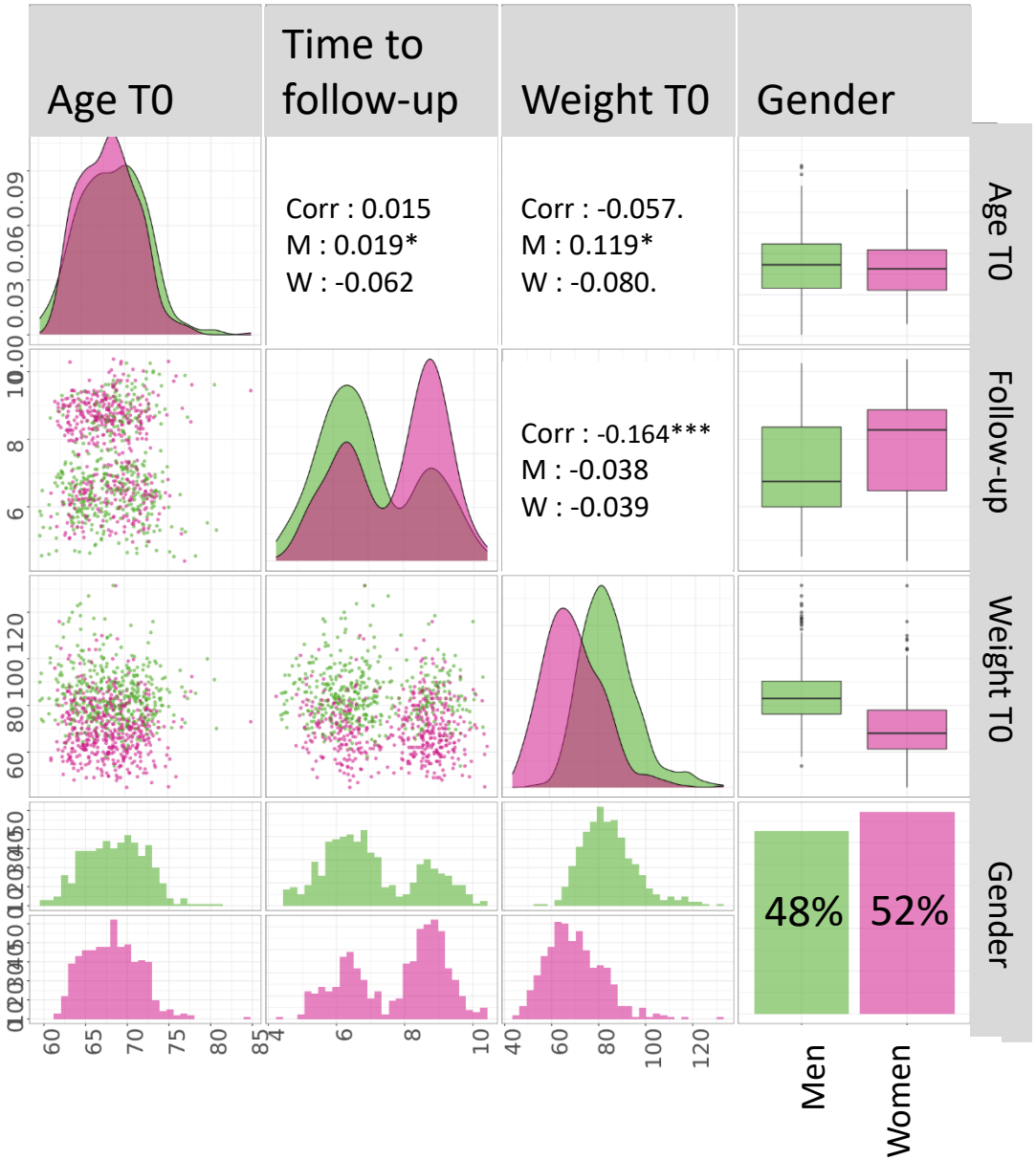

68,3 years ± 3,5 years

⇒ Bimodality according to gender

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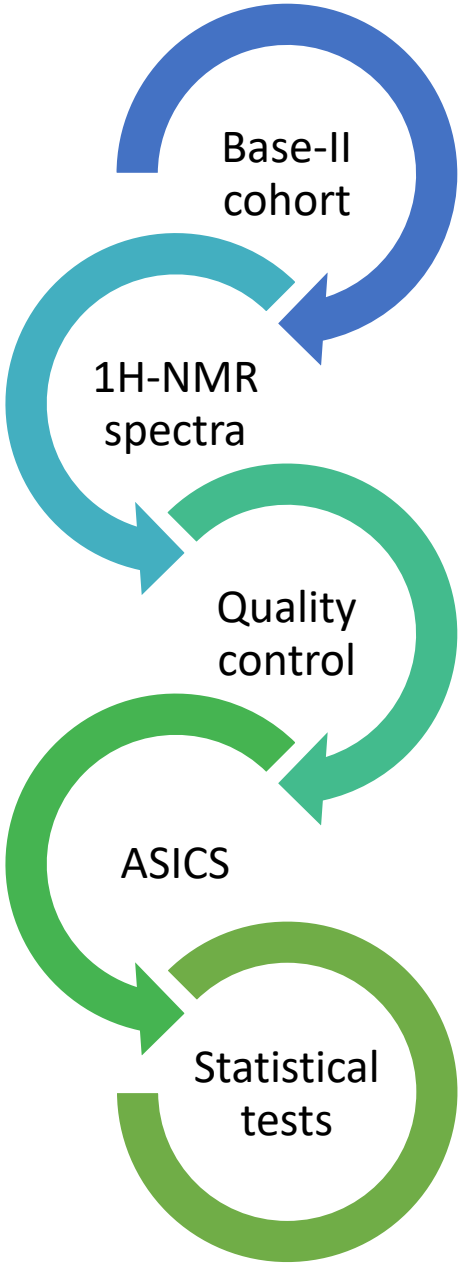

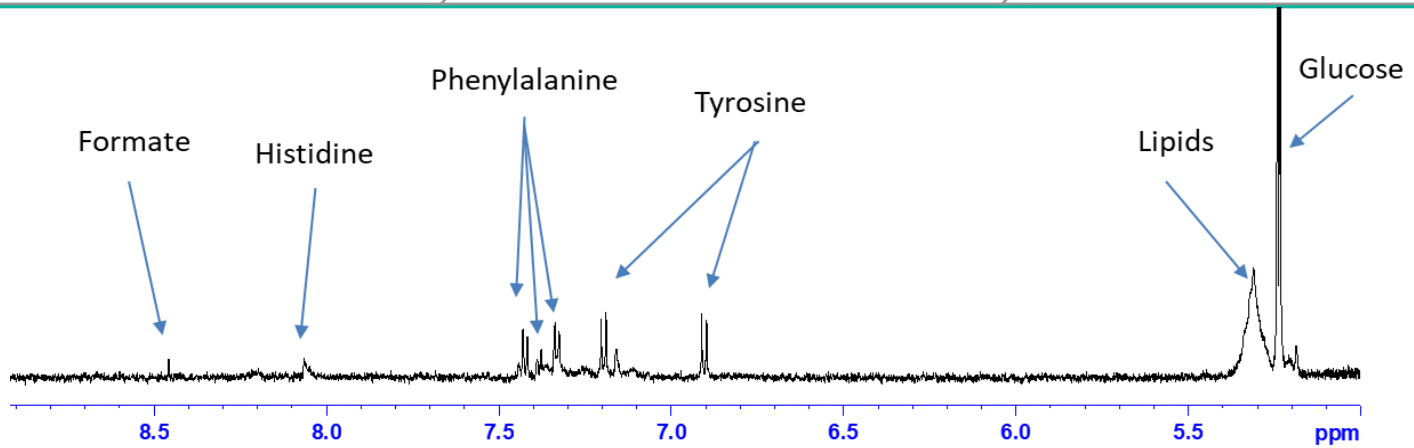

INRAE

Genotoul Metatoul AXIOM

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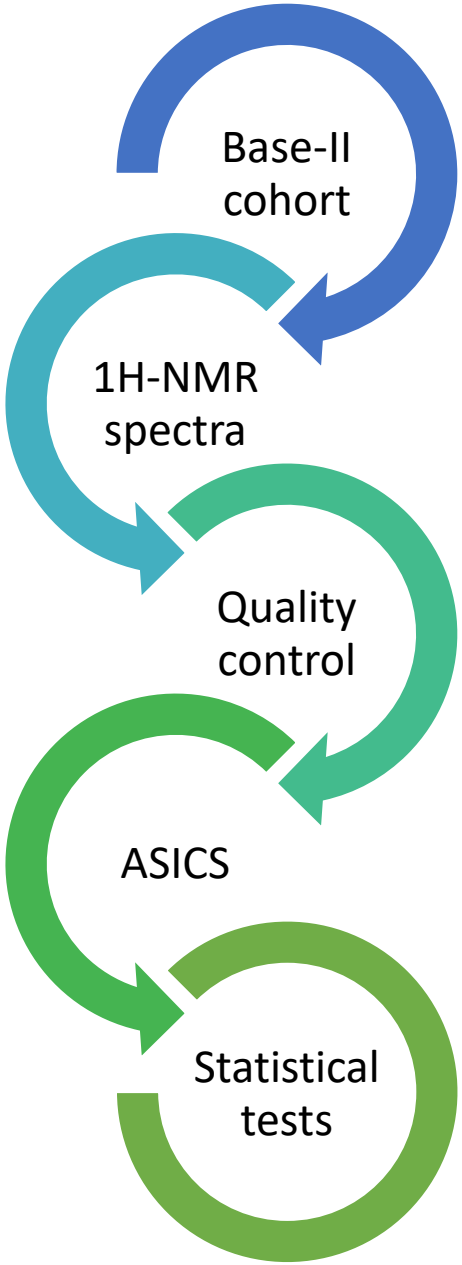

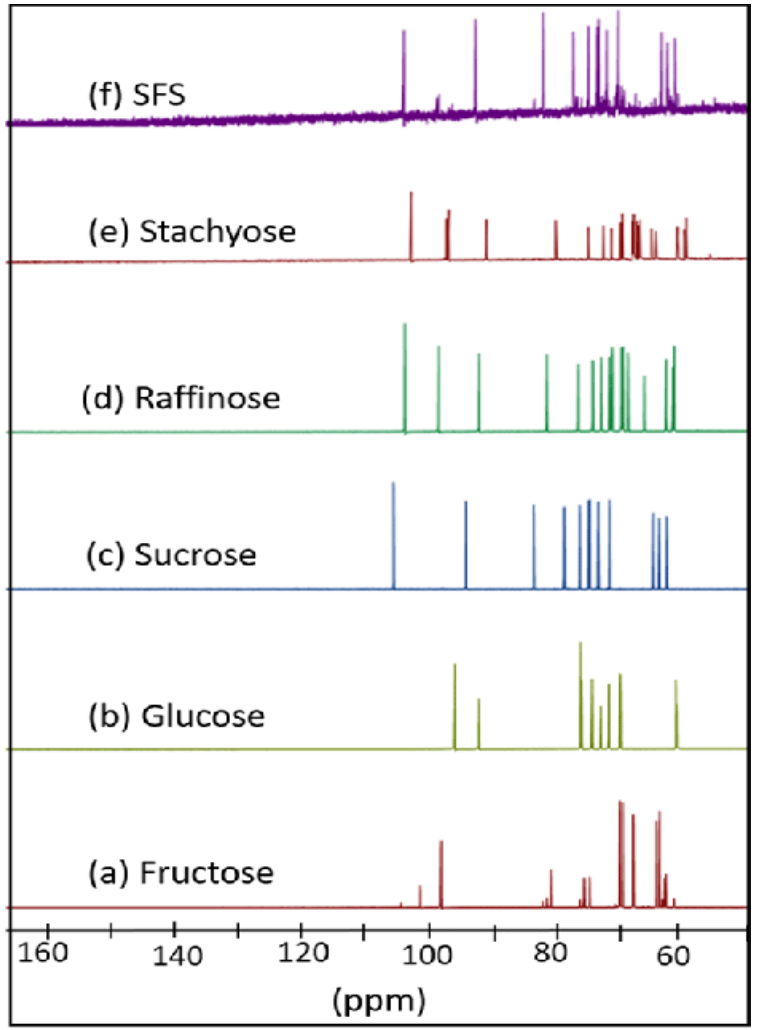

13 C NMR spectra of (a) fructose, (b) glucose, (c) sucrose, (d) raffinose, (e) stachyose, and (f) SFS.
Extracted from Patil, Namrata & Netravali, Anil. (2019)

~ 200 pure spectra of 1H NMR spectra in ASICS

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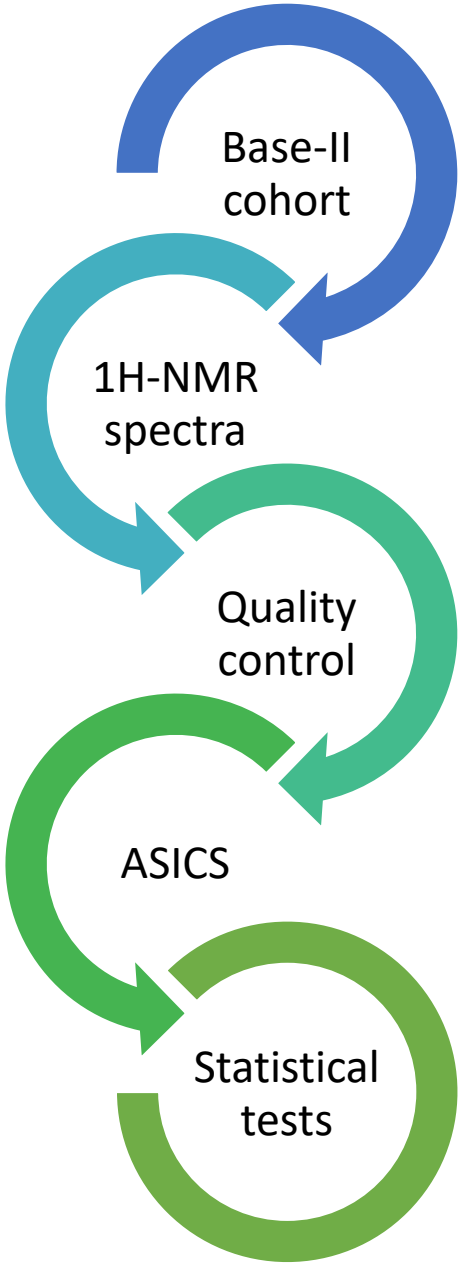

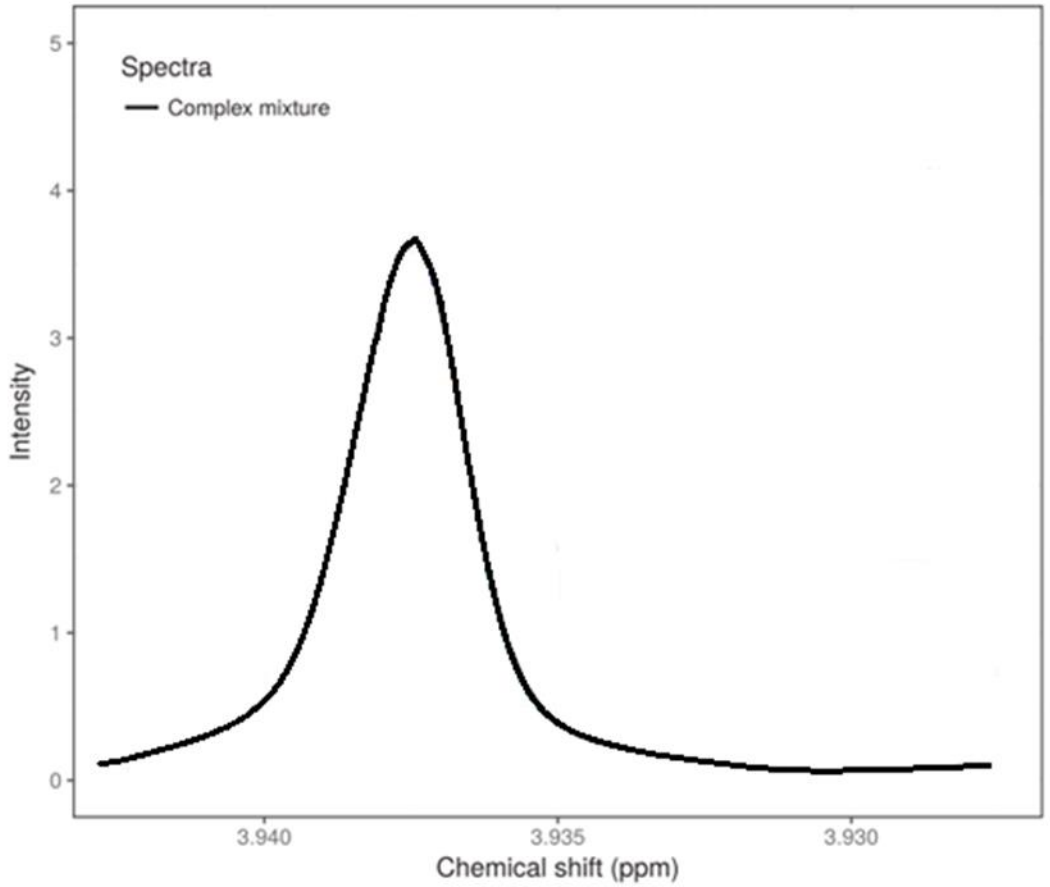

Fig. 2. Two steps distortion procedure for the main peak of the creatine. ① Global translation of the creatine spectrum. ② Local distortion of one of the creatine peak

INRAE

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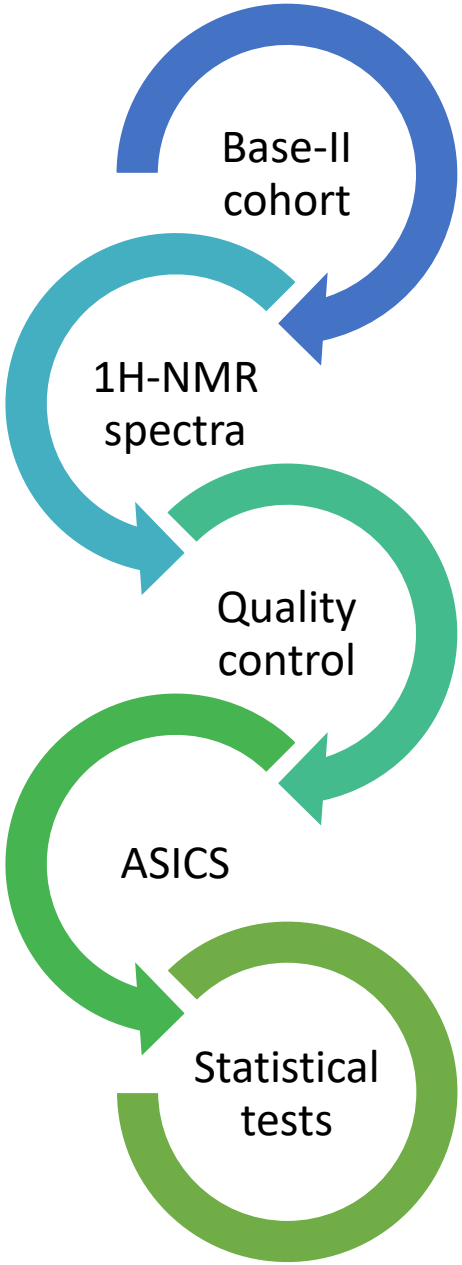

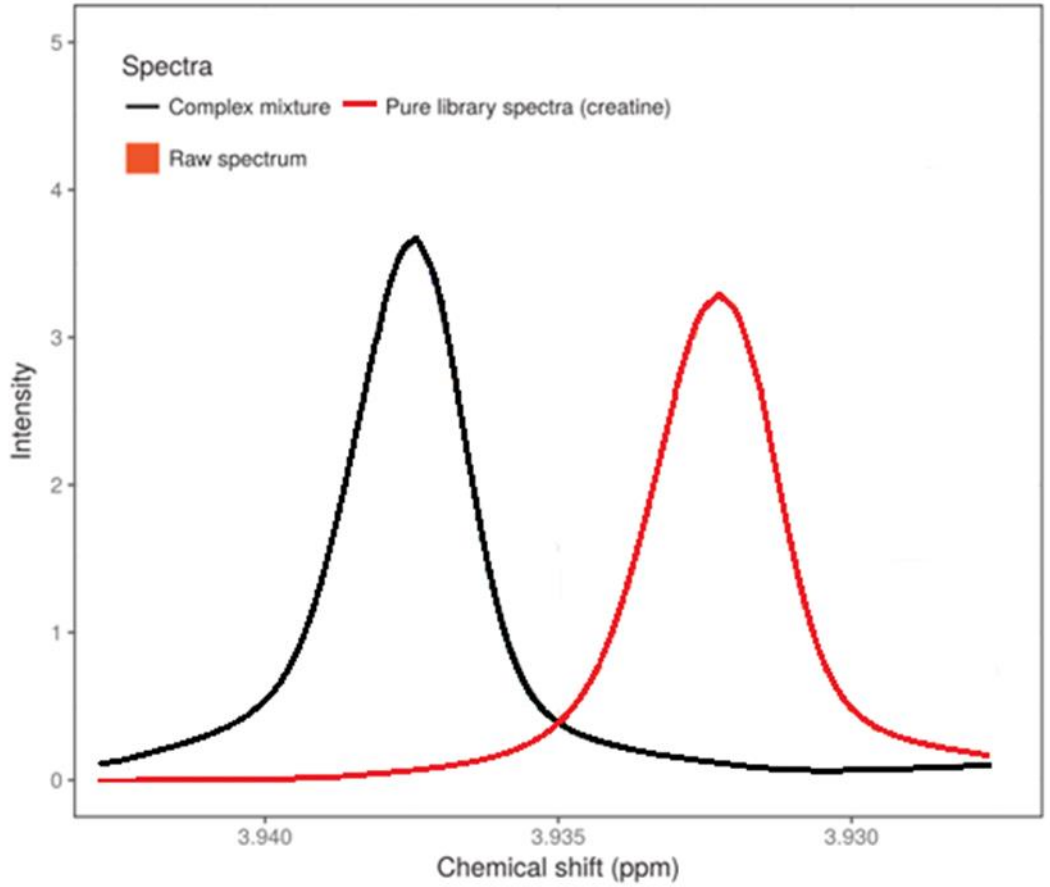

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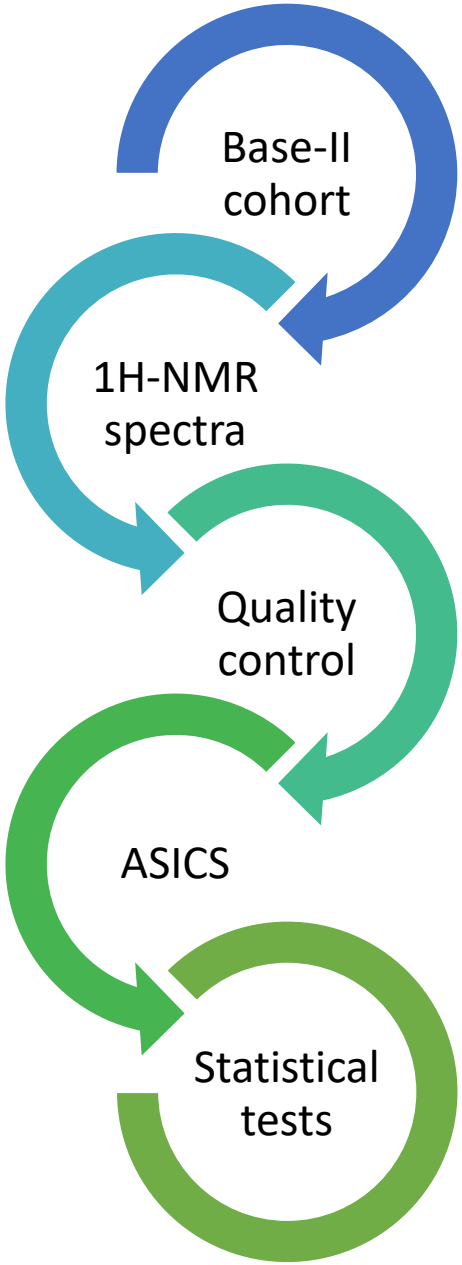

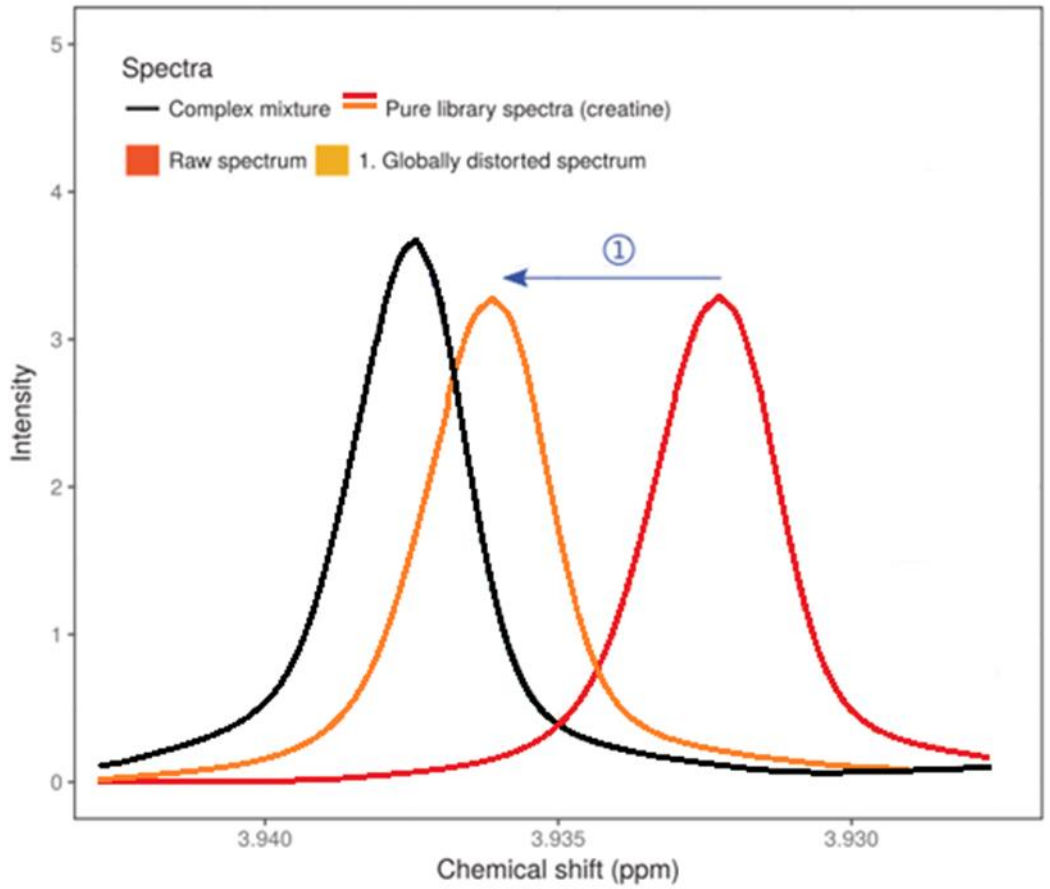

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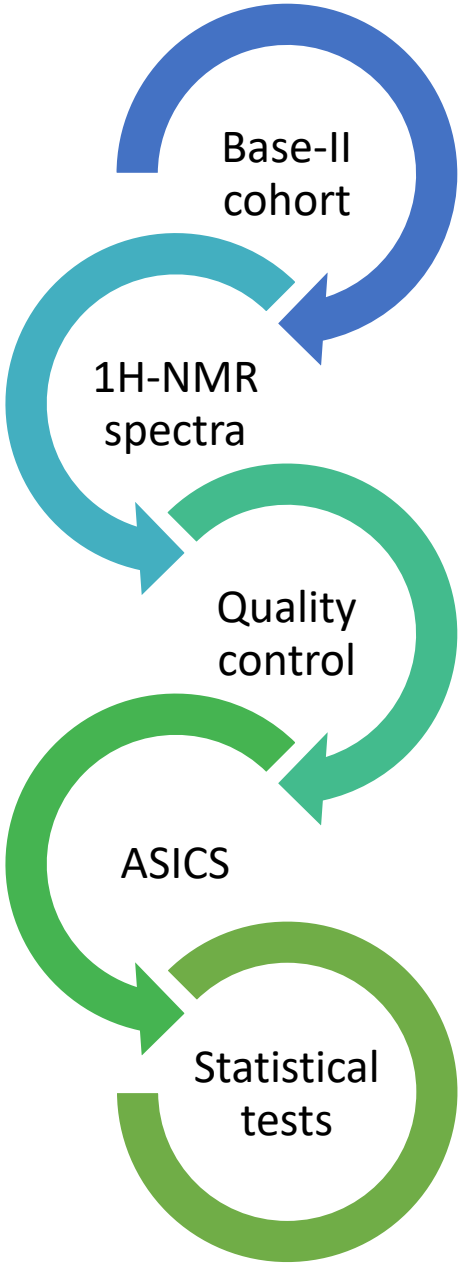

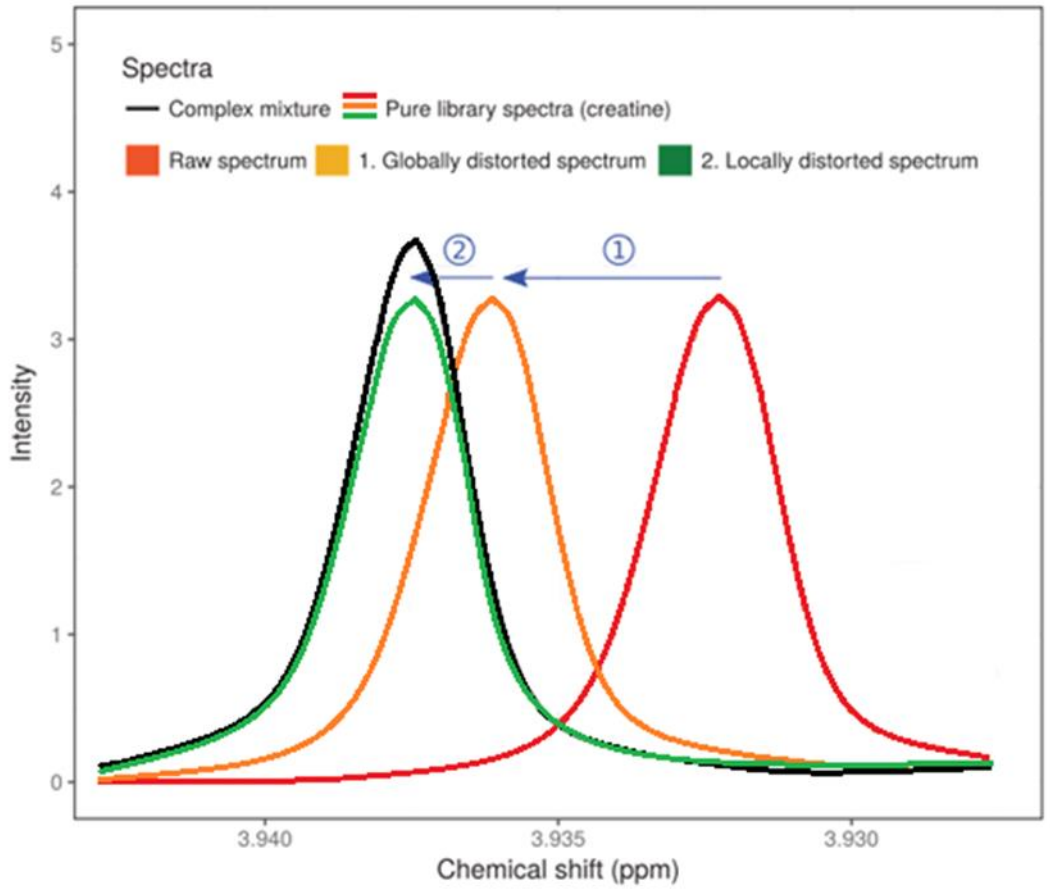

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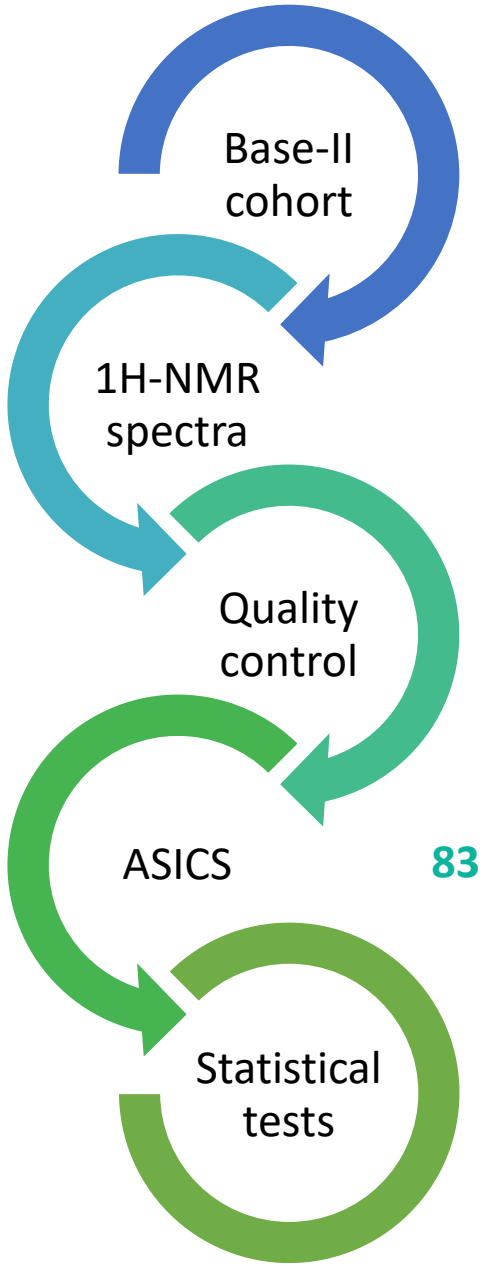

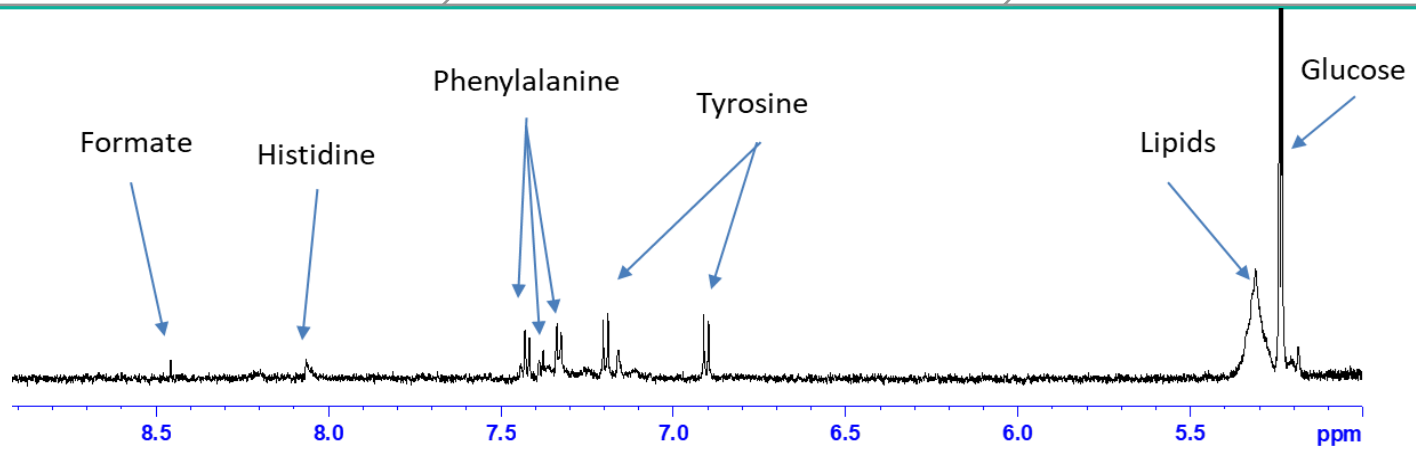

901 subjects

83 metabolites

	211001184-0001	211001184-0002	211001184-0004	211001184-0005	211001184-0006	211001184-0007	…
D_Glucose	0.053637504	0.0269908876	0.074241899	0.0532884023	0.056823830	0.052105032	
Lactate	0.025744483	0.0137337715	0.033183863	0.0235813410	0.030771858	0.015871980	
L_Glycine	0.007335422	0.0021609698	0.005943973	0.0037103629	0.006243144	0.005031519	
L_Proline	0.006793431	0.0031346472	0.008011630	0.0046917477	0.006056754	0.005878591	
EthylmalonicAcid	0.006611386	0.0013646610	0.004731661	0.0017133684	0.004892053	0.005126834	
L_Alanine	0.005964911	0.0034611321	0.007756894	0.0051744429	0.006054566	0.004886721	
M2_HydroxybutyricAcid	0.005105685	0.0007250717	0.002684368	0.0005777885	0.002840396	0.002043006	
SebacicAcid	0.004506666	0.0008176683	0.002354617	0.0007221891	0.002892575	0.002283709	
DehydroAscorbicAcid	0.003578119	0.0017121190	0.004691496	0.0027102315	0.004129003	0.003595136	
⋮							

Quantifications

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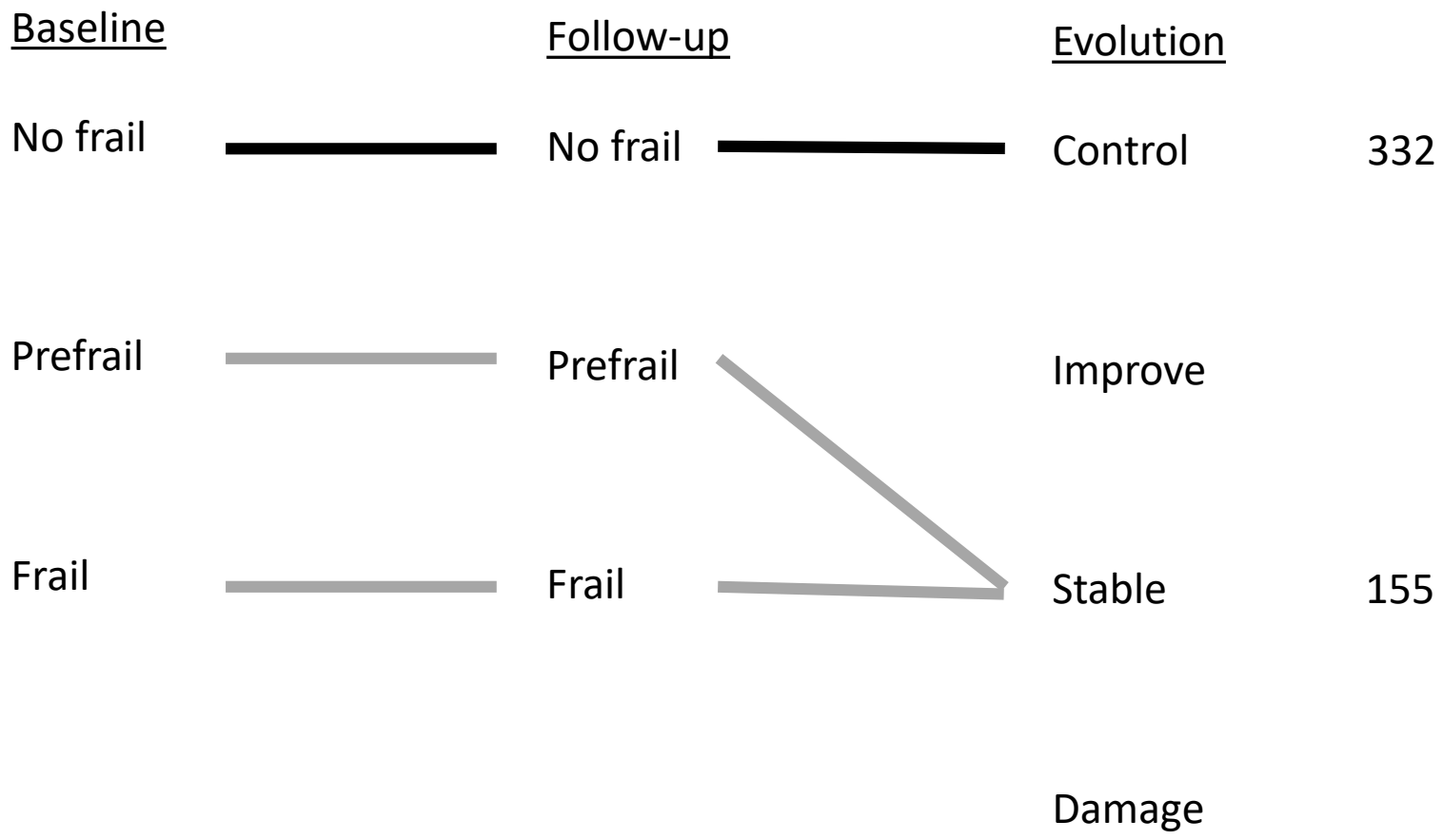
Definition of frailty evolution:

Baseline	Follow-up	Evolution
No frail	No frail	Control
Prefrail	Prefrail	Improve
Frail	Frail	Stable
		Damage

Definition of frailty evolution:

Baseline	Follow-up	Evolution	
No frail	No frail	Control	332
Prefrail	Prefrail	Improve	
Frail	Frail	Stable	
		Damage	

Definition of frailty evolution:



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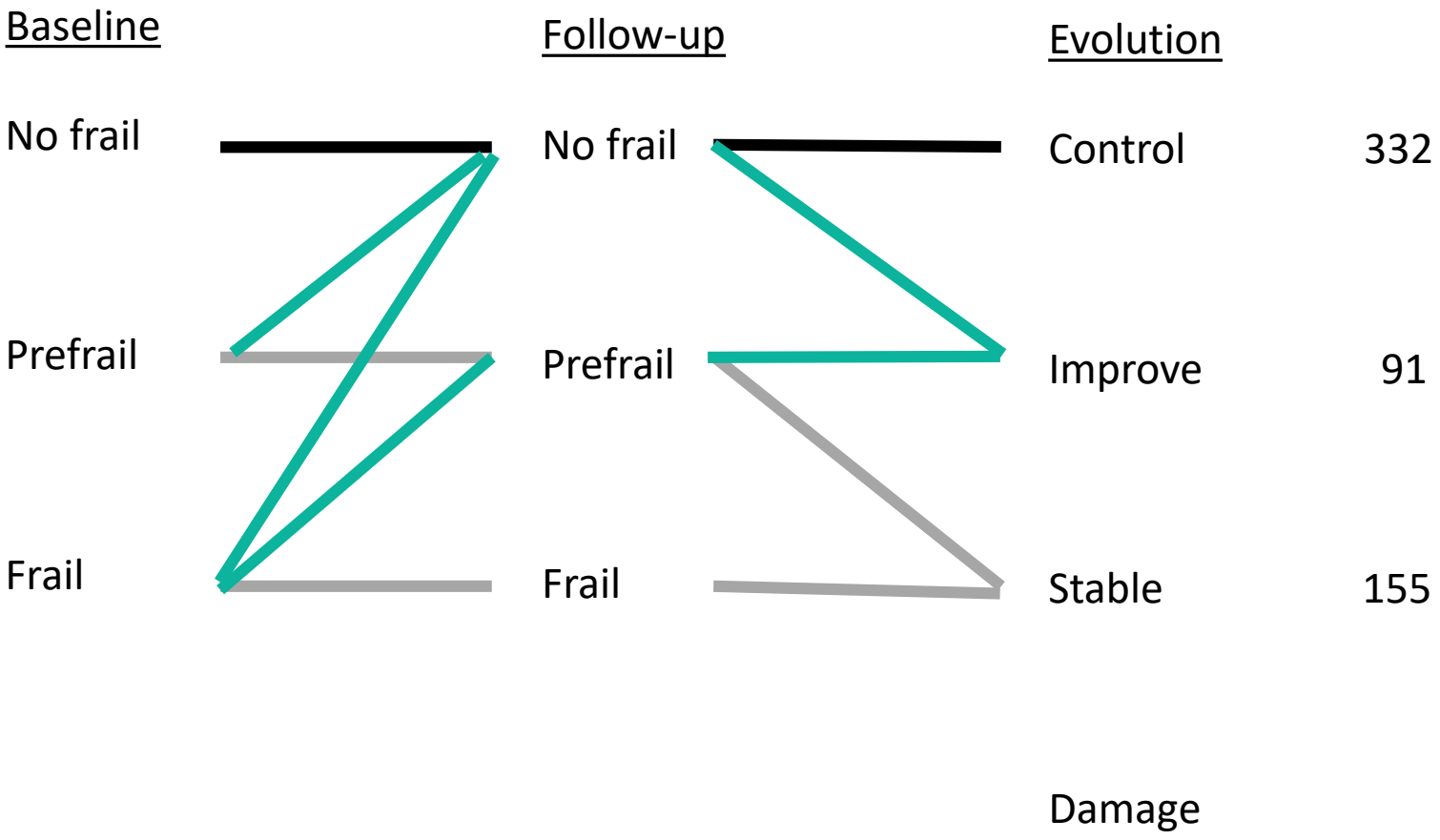
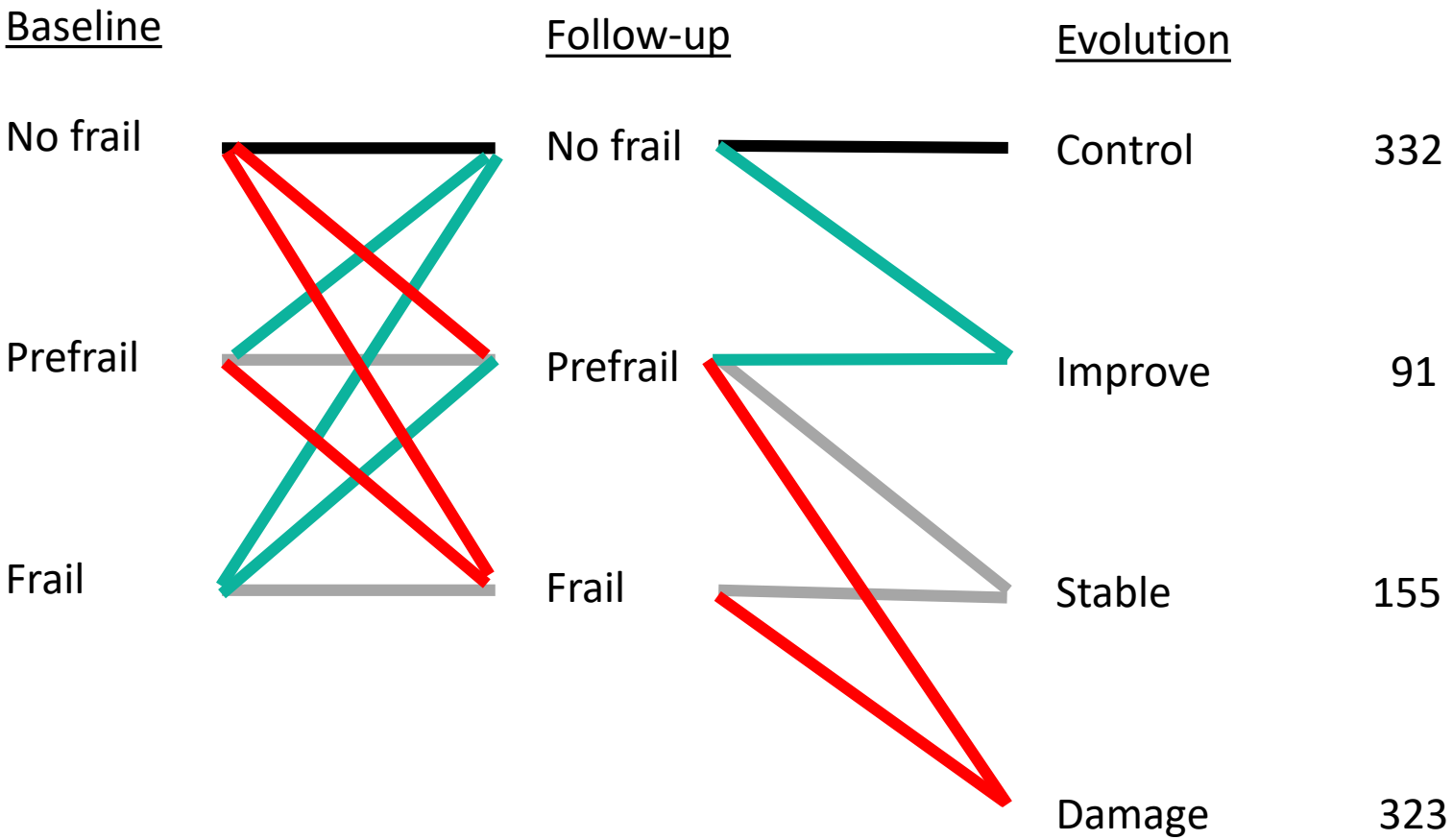


Definition of frailty evolution:



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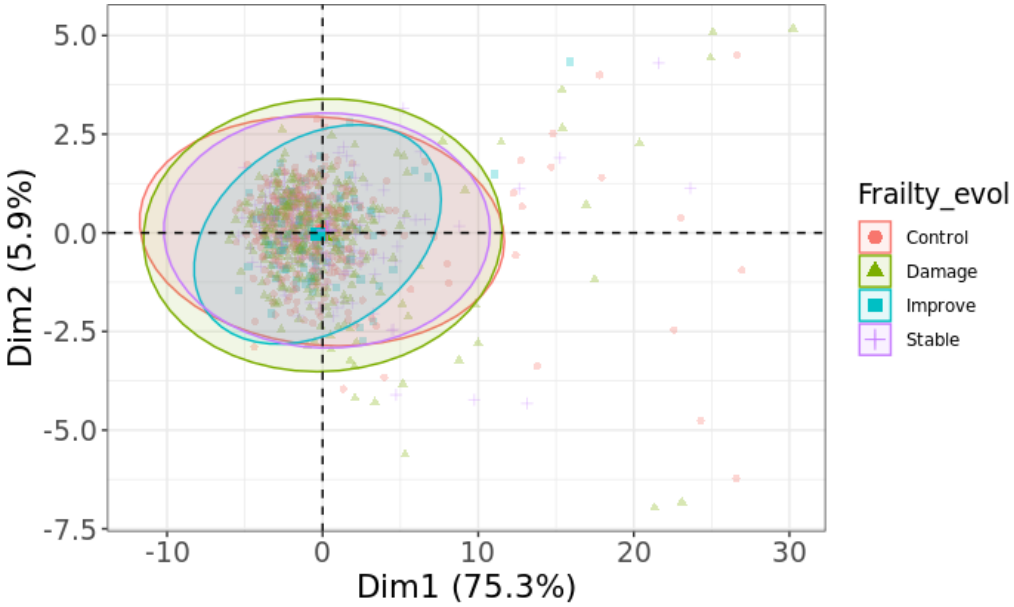
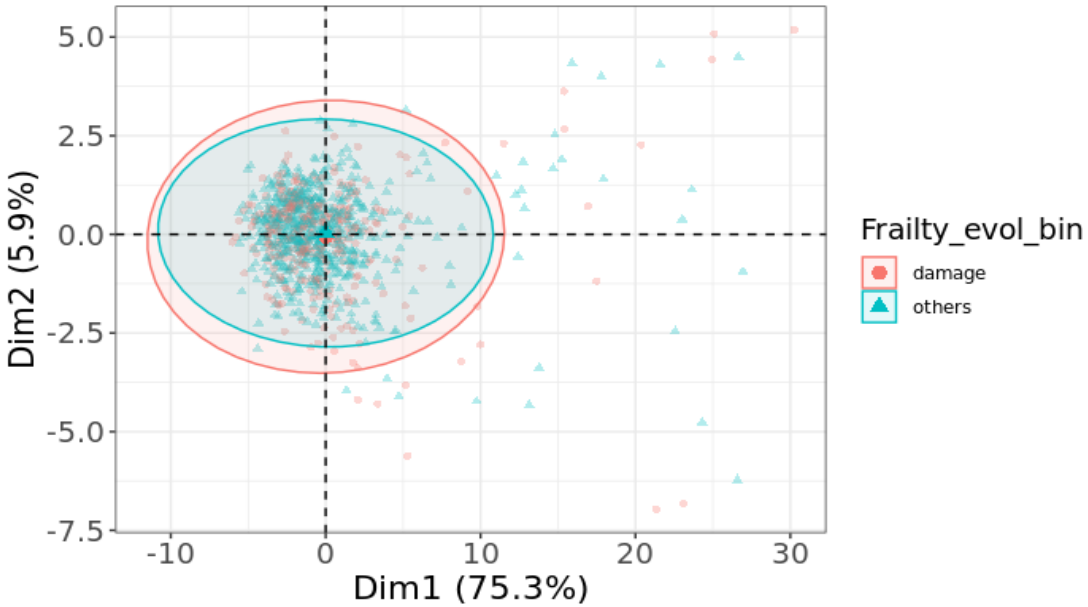
PCA on quantifications:





⇒ Homogeneous population

⇒ Weak signal on frailty

1

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Which metabolites exhibit a significant interaction effect between frailty and gender?	
Tested outcomes	**All population (N = 901 subjects)**
Frailty evolution	
Frailty evolution binary	
Frailty T0 binary	
Frailty T7 binary	
Grip T0	
Grip T7	
Grip evolution	
Grip abs Var	
Grip binary T0	
Grip binary T7	
CES-D T0	
CES-D T7	
CES-D evolution	
CES-D abs Var	
CES-D binary T0	
CES-D binary T7	
MNA score T0	
MNA score T7	
MNA binary T0	
MNA binary T7	

Linear models:

$H1 : Quantif_i \sim \beta_0 + outcome_i + gender_i + outcome_i*gender_i + ageDiff_i + age\_T0_i + weight\_T0_i + \varepsilon_i$

$H0 : Quantif_i \sim \beta_0 + outcome_i + gender_i + ageDiff_i + age\_T0_i + weight\_T0_i + \varepsilon_i$

1

2

3

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Frailty T7 binary	
Grip T0	
Grip T7	
Grip evolution	
Grip abs Var	
Grip binary T0	
Grip binary T7	
CES-D T0	
CES-D T7	
CES-D evolution	
CES-D abs Var	
CES-D binary T0	
CES-D binary T7	
MNA score T0	
MNA score T7	
MNA binary T0	
MNA binary T7	

Linear models:

$H1 : Quantif_i \sim \beta_0 + outcome_i + gender_i + outcome_i*gender_i + ageDiff_i + age\_T0_i + weight\_T0_i + \varepsilon_i$

$H0 : Quantif_i \sim \beta_0 + outcome_i + gender_i + ageDiff_i + age\_T0_i + weight\_T0_i + \varepsilon_i$

No significant interaction effect between frailty and gender on the metabolome.

1

2

3

Which metabolites have significantly different quantifications according to frailty, for men and women respectively?		
Tested outcomes	**Men (N = 428 subjects)**	**Women (N = 473 subjects)**
Frailty evolution		
Frailty evolution binary		
Frailty T0 binary		
Frailty T7 binary		
Grip T0		
Grip T7		
Grip evolution		
Grip abs Var		
Grip binary T0		
Grip binary T7		
CES-D T0		
CES-D T7		
CES-D evolution		
CES-D abs Var		
CES-D binary T0		
CES-D binary T7		
MNA score T0		
MNA score T7		
MNA binary T0		
MNA binary T7		

Linear models:

$H1 : Quantif_i \sim \beta_0 + outcome_i + ageDiff_i + age\_T0_i + weight\_T0_i + \varepsilon_i$

$H0 : Quantif_i \sim \beta_0 + ageDiff_i + age\_T0_i + weight\_T0_i + \varepsilon_i$

1

2

3

Which metabolites have significantly different quantifications according to frailty, for men and women respectively?

Tested outcomes	Men (N = 428 subjects)	Women (N = 473 subjects)
Frailty evolution		
Frailty evolution binary		
Frailty T0 binary		
Frailty T7 binary		
Grip T0	27 metabolites	
Grip T7	31 metabolites	
Grip evolution		Dimethylsulfone
Grip abs Var		
Grip binary T0		
Grip binary T7		
CES-D T0		
CES-D T7		
CES-D evolution		
CES-D abs Var		
CES-D binary T0		
CES-D binary T7		
MNA score T0		
MNA score T7		
MNA binary T0	21 metabolites	
MNA binary T7		

Linear models:

$H1 : Quantif_i \sim \beta_0 + outcome_i + ageDiff_i + age\_T0_i + weight\_T0_i + \varepsilon_i$

$H0 : Quantif_i \sim \beta_0 + ageDiff_i + age\_T0_i + weight\_T0_i + \varepsilon_i$

1

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3

Which metabolites have significantly different quantifications according to frailty, for men and women respectively?

Tested outcomes	Men (N = 428 subjects)	Women (N = 473 subjects)
Frailty evolution		
Frailty evolution binary		
Frailty T0 binary		
Frailty T7 binary		
Grip T0	27 metabolites	
Grip T7	31 metabolites	
Grip evolution		Dimethylsulfone
Grip abs Var		
Grip binary T0		
Grip binary T7		
CES-D T0		
CES-D T7		
CES-D evolution		
CES-D abs Var		
CES-D binary T0		
CES-D binary T7		
MNA score T0		
MNA score T7		
MNA binary T0	21 metabolites	
MNA binary T7		

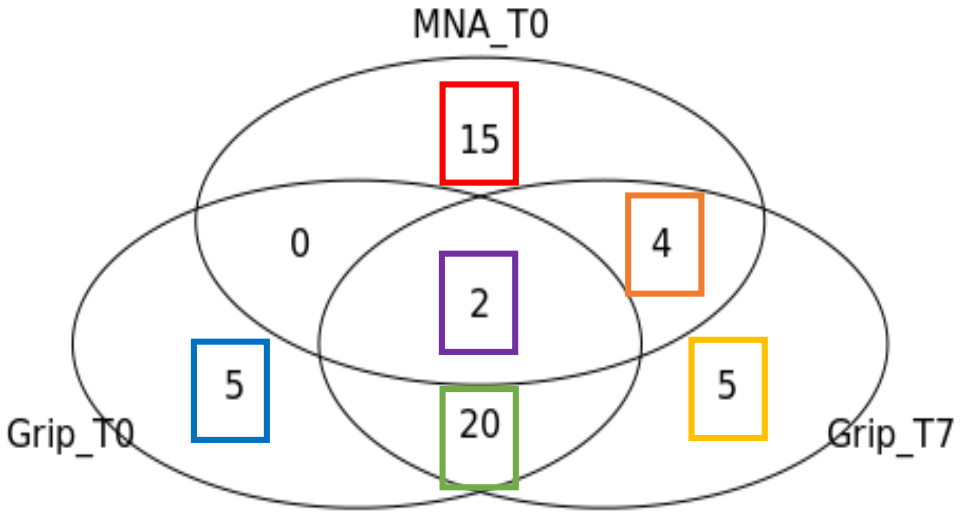
Metabolism of inositol phosphate

Catabolism of branched chain amino acids

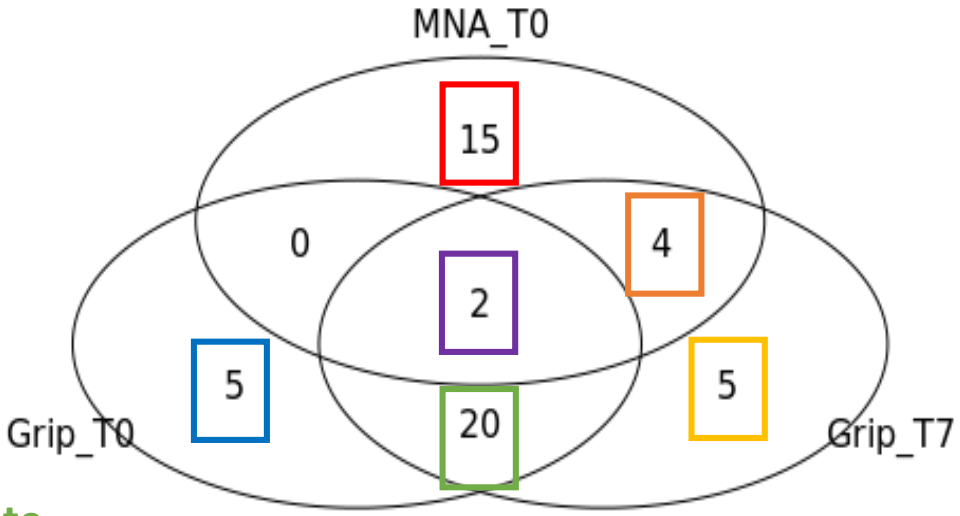
Linear models:

$H1 : Quantif_i \sim \beta_0 + outcome_i + ageDiff_i + age\_T0_i + weight\_T0_i + \varepsilon_i$

$H0 : Quantif_i \sim \beta_0 + ageDiff_i + age\_T0_i + weight\_T0_i + \varepsilon_i$

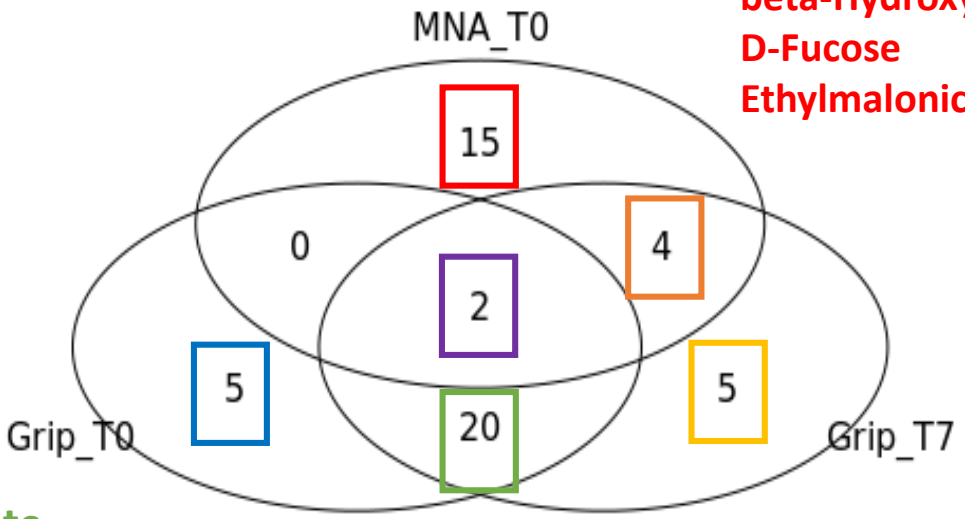

MNA_T0
15
0
4
2
5
5
20
Grip_T0
Grip_T7

Betaine
1,3-Diaminopropane



D-Maltose	Lactate
L-Cystine	PropyleneGlycol
Myo-Inositol	D-GlucuronicAcid
GlycericAcid	3-Methylxanthine
L-GlutamicAcid	D-Glucose
L-Methionine	GuanidinoaceticAcid
D-Mannose	DehydroAscorbicAcid
Taurine	L-Carnitine
Galactitol	Levoglucosan
D-Fructose	7-Methylxanthine"

Betaine
1,3-Diaminopropane



2-HydroxybutyricAcid
2-Oxoisovalerate
3-PhenylPropionicAcid
alpha-HydroxyisobutyricAcid
beta-HydroxyisovalericAcid
D-Fucose
EthylmalonicAcid

GABA
IsovalericAcid
L-Isoleucine
Lactose
MethylmalonicAcid
PyroglutamicAcid
SebacicAcid
Valerate

D-Maltose
L-Cystine
Myo-Inositol
GlycericAcid
L-GlutamicAcid
L-Methionine
D-Mannose
Taurine
Galactitol
D-Fructose

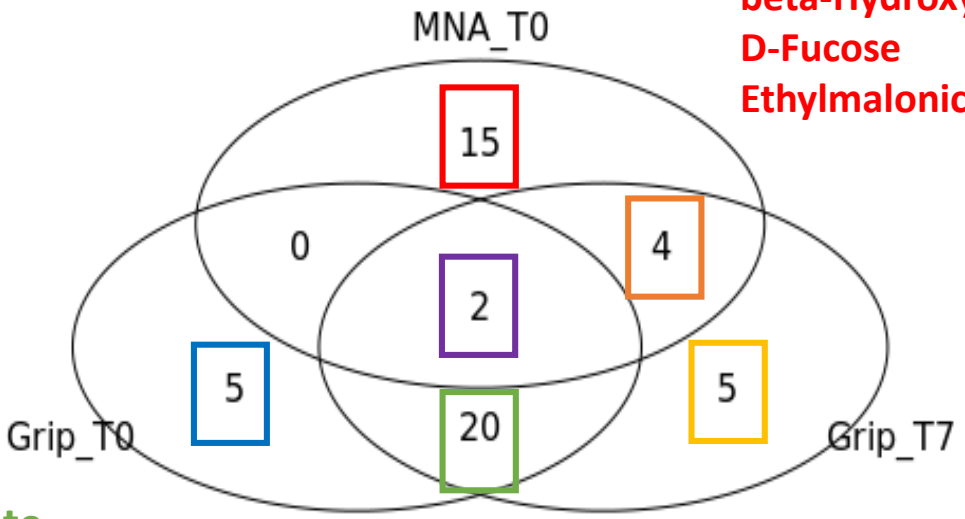
Lactate
PropyleneGlycol
D-GlucuronicAcid
3-Methylxanthine
D-Glucose
GuanidinoaceticAcid
DehydroAscorbicAcid
L-Carnitine
Levoglucosan
7-Methylxanthine"

Betaine
1,3-Diaminopropane

2-HydroxybutyricAcid
2-Oxoisovalerate
3-PhenylPropionicAcid
alpha-HydroxyisobutyricAcid
beta-HydroxyisovalericAcid
D-Fucose
EthylmalonicAcid

GABA
IsovalericAcid
L-Isoleucine
Lactose
MethylmalonicAcid
PyroglutamicAcid
SebacicAcid
Valerate

Beta-Alanine
L-Lysine
L-Serine
MalicAcid
O-Acetyl-L-Carnitine

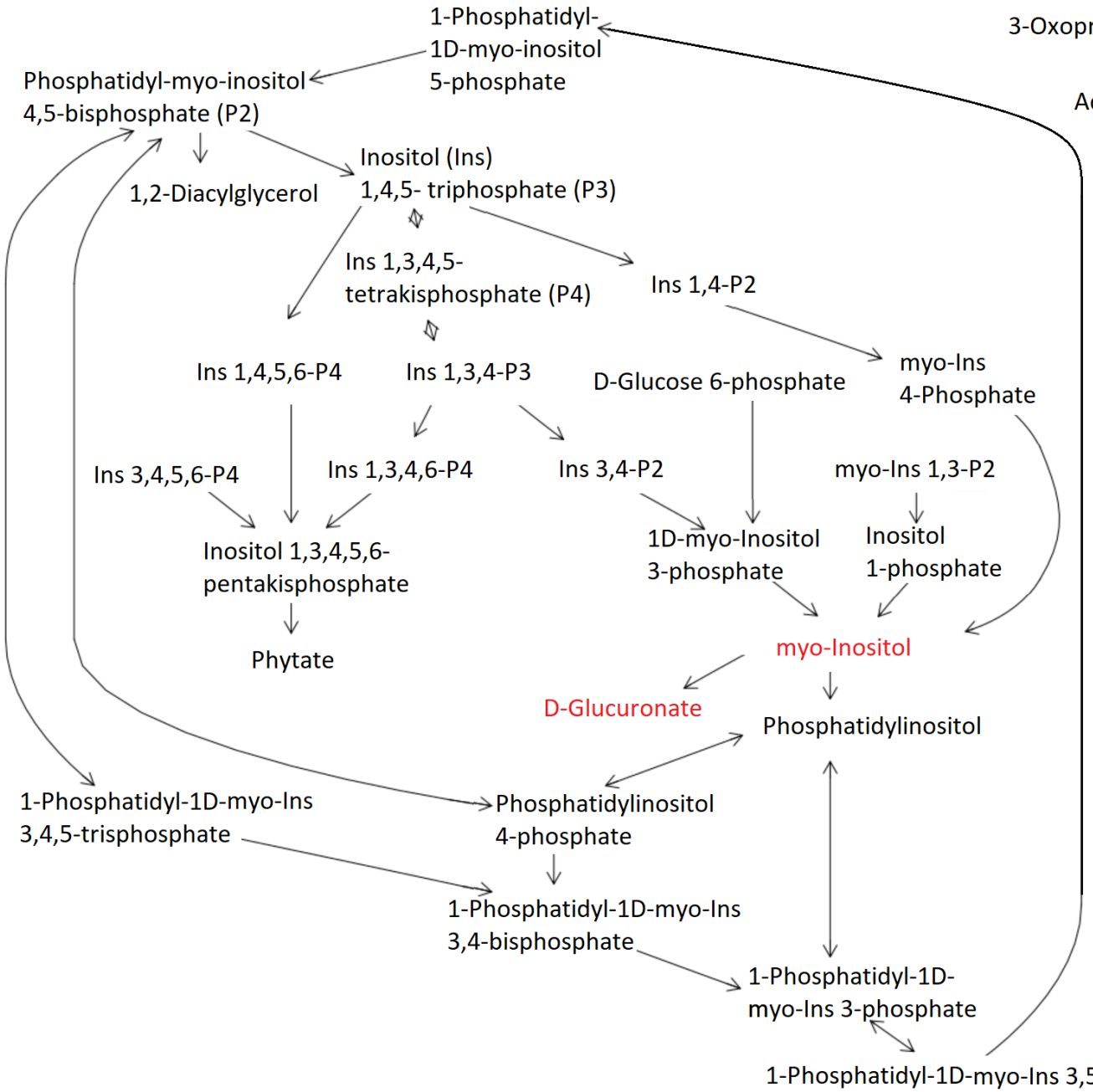


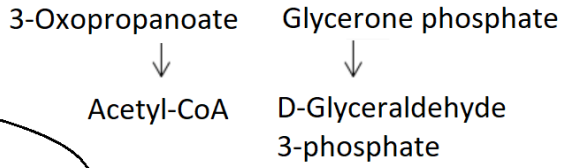
2-Oxoglutarate
PantothenicAcid
L-Aspartate
N-Acetylglycine

D-Maltose
L-Cystine
Myo-Inositol
GlycericAcid
L-GlutamicAcid
L-Methionine
D-Mannose
Taurine
Galactitol
D-Fructose

Lactate
PropyleneGlycol
D-GlucuronicAcid
3-Methylxanthine
D-Glucose
GuanidinoaceticAcid
DehydroAscorbicAcid
L-Carnitine
Levoglucosan
7-Methylxanthine"

L-Valine
Putrescine
TMAO
L-Tyrosine
L-Threonine

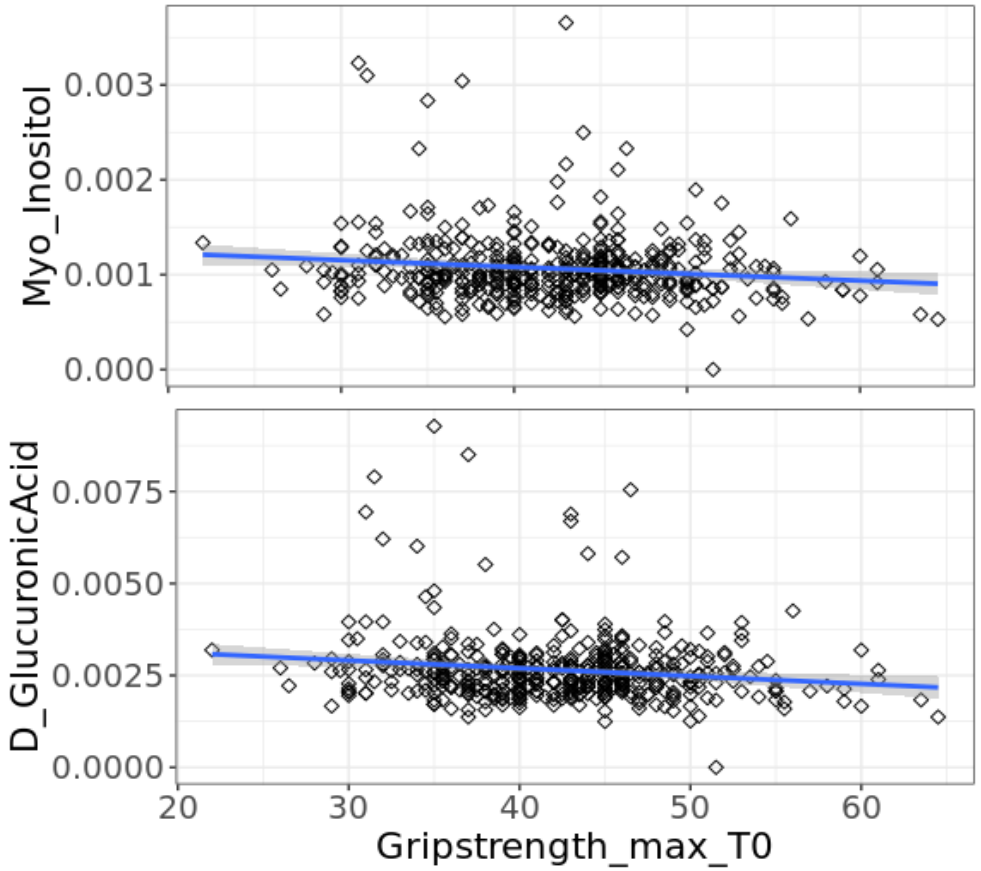

1-Phosphatidyl-
1D-myo-inositol
5-phosphate
Phosphatidyl-myo-inositol
4,5-bisphosphate (P2)
1,2-Diacylglycerol
Inositol (Ins)
1,4,5- triphosphate (P3)
Ins 1,3,4,5-
tetrakisphosphate (P4)
Ins 1,4-P2
Ins 1,4,5,6-P4
Ins 1,3,4-P3
D-Glucose 6-phosphate
myo-Ins
4-Phosphate
Ins 3,4,5,6-P4
Ins 1,3,4,6-P4
Ins 3,4-P2
myo-Ins 1,3-P2
Inositol 1,3,4,5,6-
pentakisphosphate
1D-myo-Inositol
3-phosphate
Inositol
1-phosphate
Phytate
myo-Inositol
D-Glucuronate
Phosphatidylinositol
1-Phosphatidyl-1D-myo-Ins
3,4,5-trisphosphate
Phosphatidylinositol
4-phosphate
1-Phosphatidyl-1D-myo-Ins
3,4-bisphosphate
1-Phosphatidyl-1D-
myo-Ins 3-phosphate
1-Phosphatidyl-1D-myo-Ins 3,5-P2

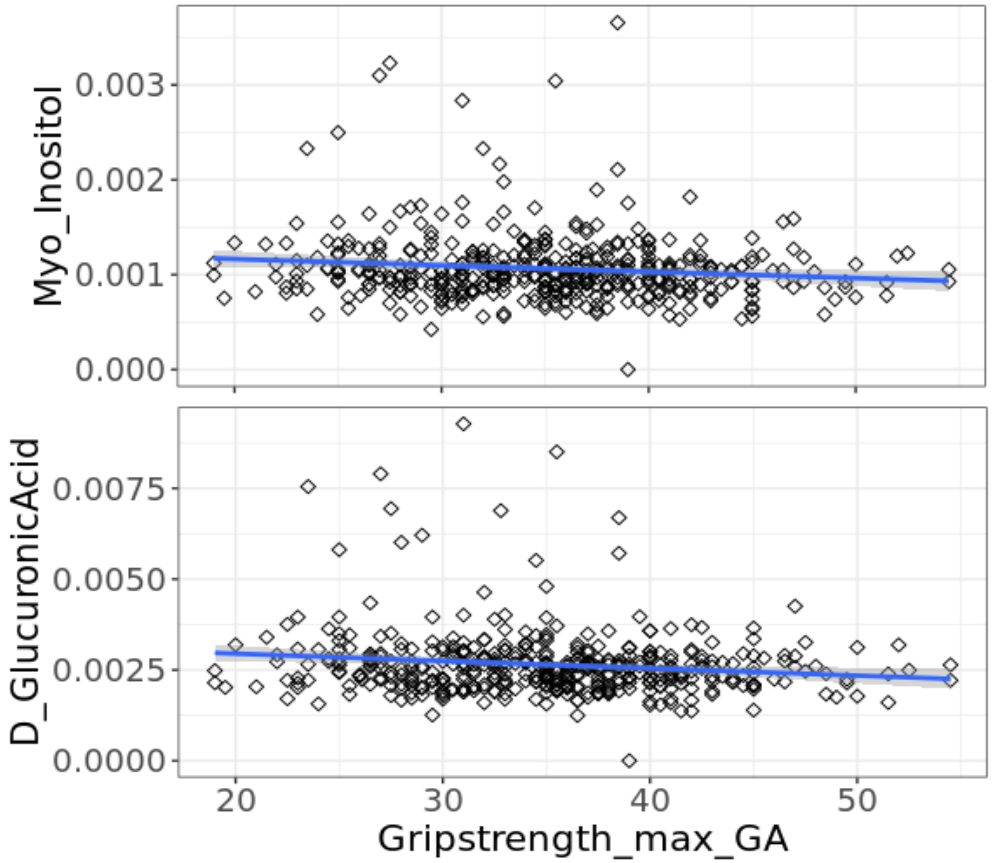

3-Oxopropanoate
Acetyl-CoA
Glycerone phosphate
D-Glyceraldehyde
3-phosphate

1

2

3


Myo_Inositol
0.003
0.002
0.001
0.000
D_GlucuronicAcid
0.0075
0.0050
0.0025
0.0000
20
30
40
50
60
Gripstrength_max_T0


Myo_Inositol
0.003
0.002
0.001
0.000
D_GlucuronicAcid
0.0075
0.0050
0.0025
0.0000
20
30
40
50
Gripstrength_max_GA

To sum up:
identification of pathways related to hand grip strength or nutritional status

Short term objectives:
- Add mobility and/or nutritional paramters
- Build a new frailty criterion
- Compare old and young metabolomic signatures

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MERCI POUR VOTRE ATTENTION!