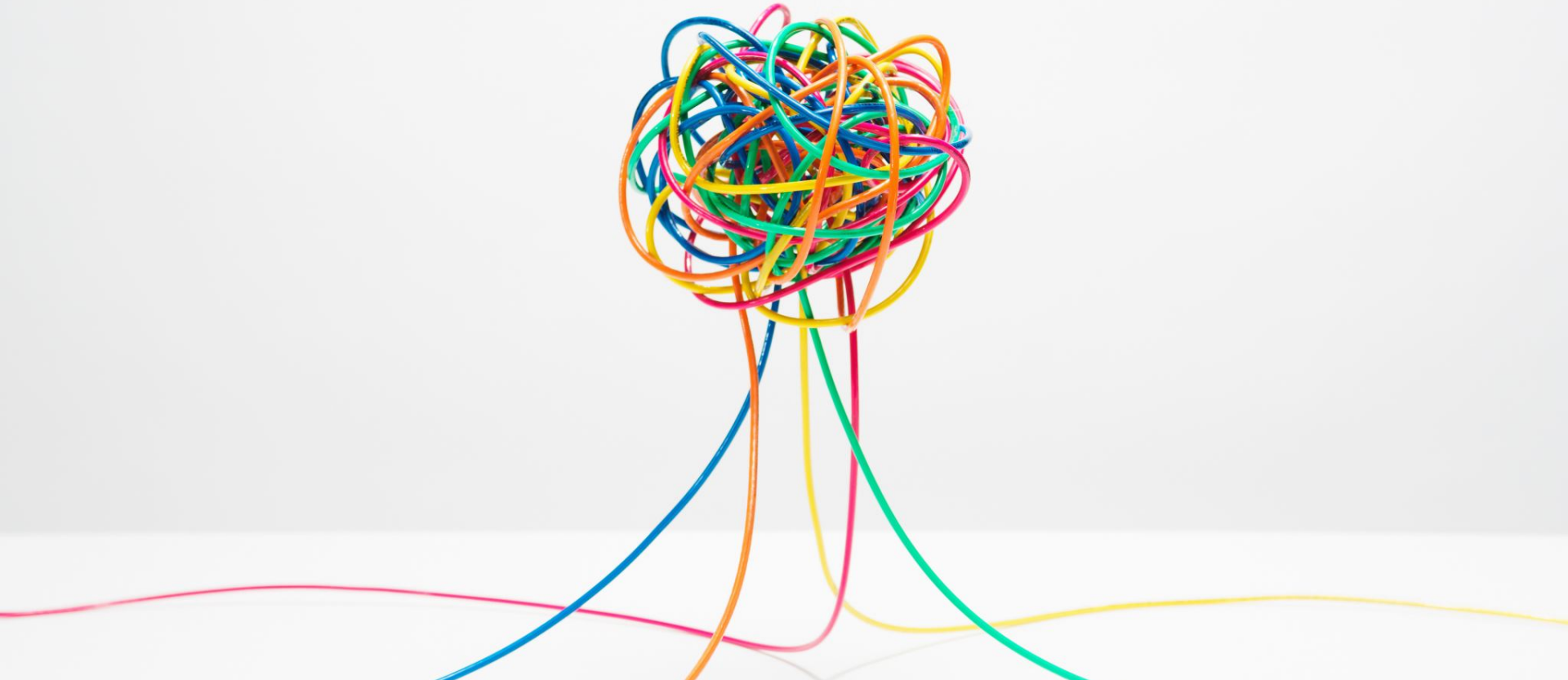
Investigating the metabolic underpinnings of early changes relevant to dementia

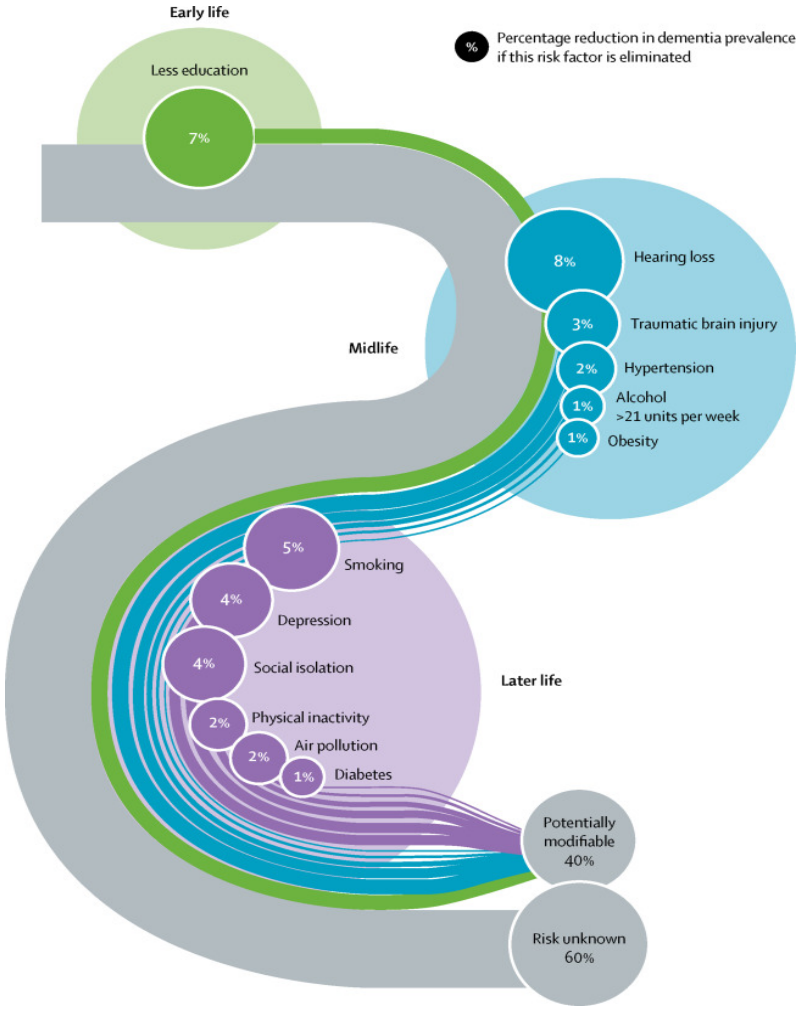
Becki Green, 3rd year PhD student, King's College London

Supervisors: Dr Petra Proitsi & Prof Marcus Richards



Dementia

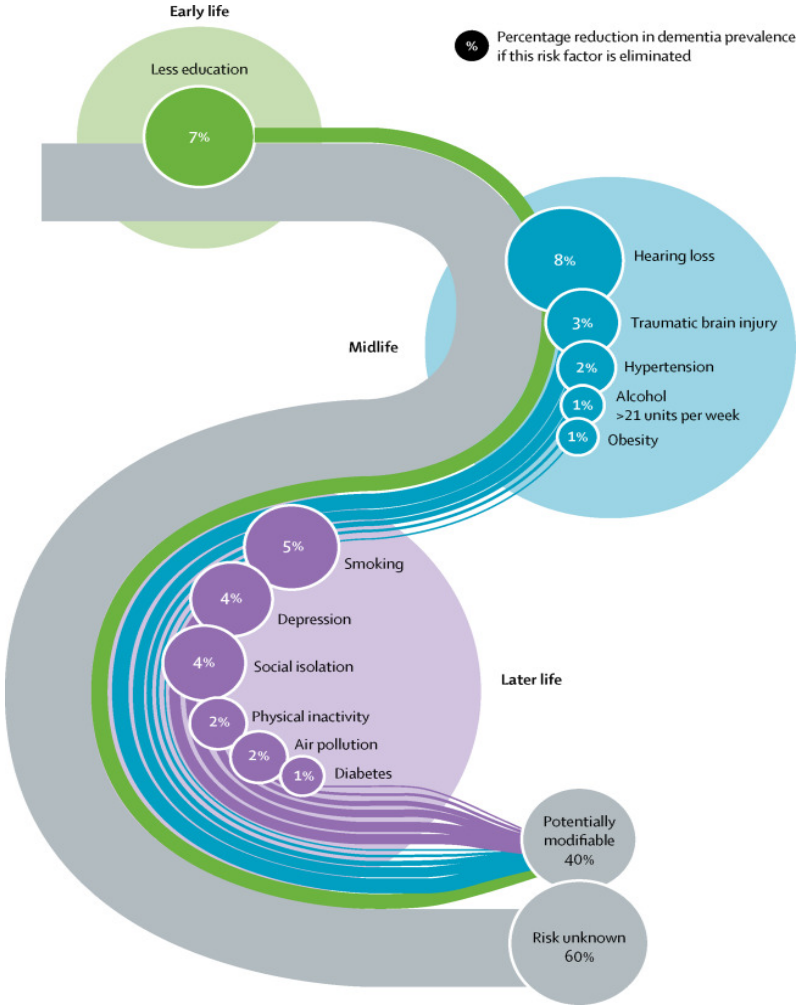
- Impairment in cognitive functioning impeding on day to day life



Livingston *et al.*, 2020

Dementia

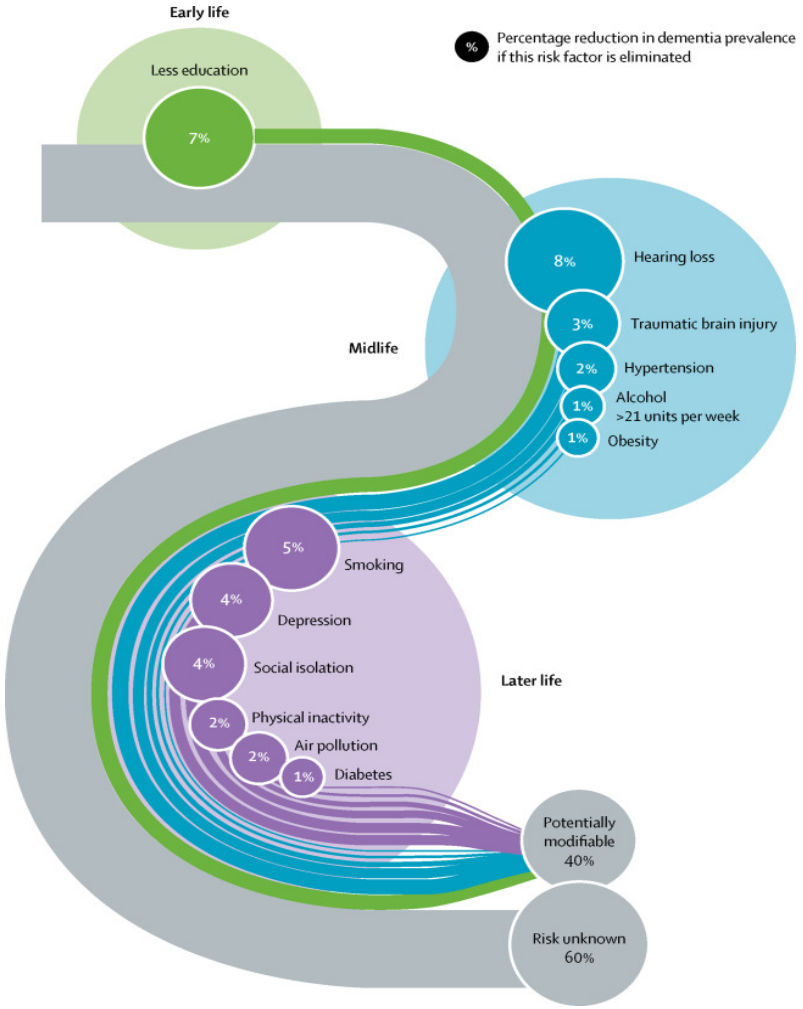
- Impairment in cognitive functioning impeding on day to day life
- 50 million people affected worldwide



Livingston *et al.*, 2020

Dementia

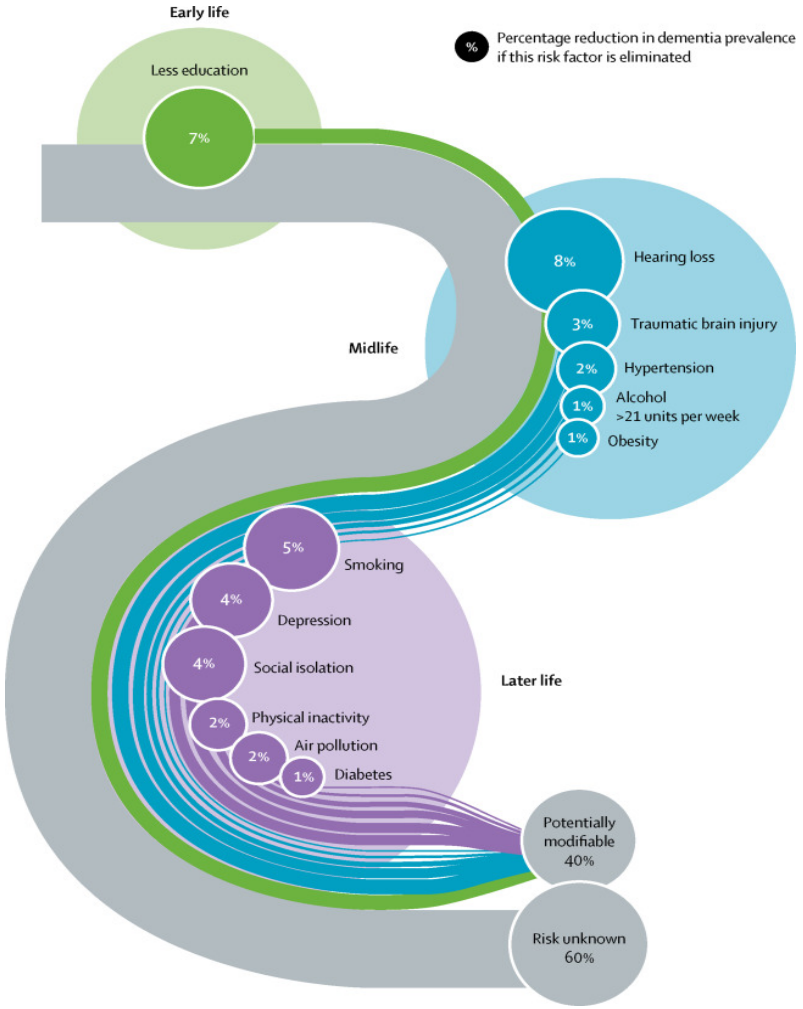
- Impairment in cognitive functioning impeding on day to day life
- 50 million people affected worldwide
- **No treatments**



Livingston *et al.*, 2020

Dementia

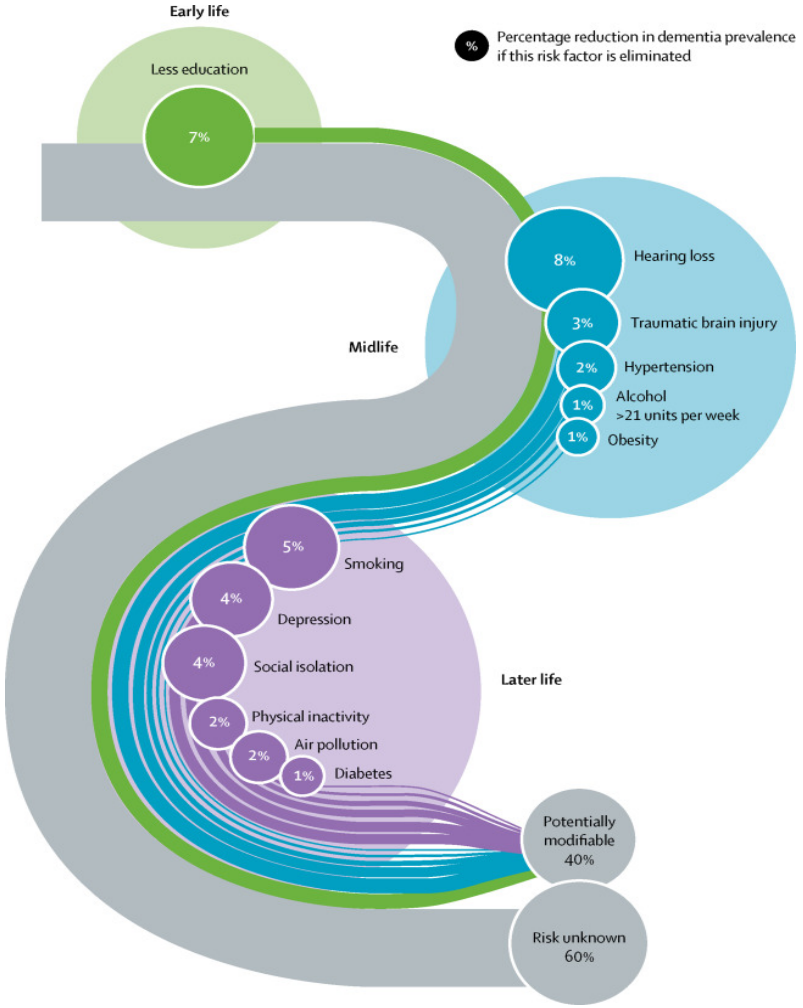
- Impairment in cognitive functioning impeding on day to day life
- 50 million people affected worldwide
- **No treatments**
- Long prodrome with lifelong influences
- = great opportunity to prevent or delay pathology



Livingston *et al.*, 2020

Dementia

- Impairment in cognitive functioning impeding on day to day life
- 50 million people affected worldwide
- **No treatments**
- Long prodrome with lifelong influences
- = great opportunity to prevent or delay pathology
- **Little known about early mechanisms**



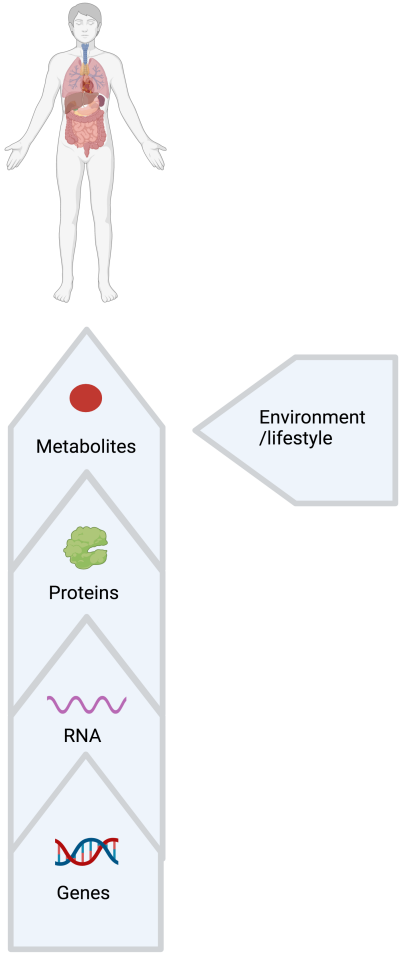
Livingston *et al.*, 2020

MRC 1946 British Birth Cohort Study | Insight 46

- World's longest continually running birth cohort
- 5362 participants born in March 1946 - LC-MS metabolomics data (N=1800), Insight 46 (brain imaging) (N=500)
- Deeply phenotyped
- Broadly representative of the population in mainland Britain at that time
- Key age

Blood metabolites

- Products of metabolism – life sustaining chemical reactions occurring in your body



Blood metabolites

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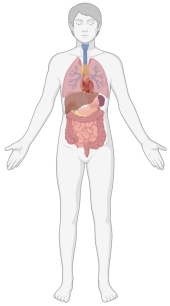

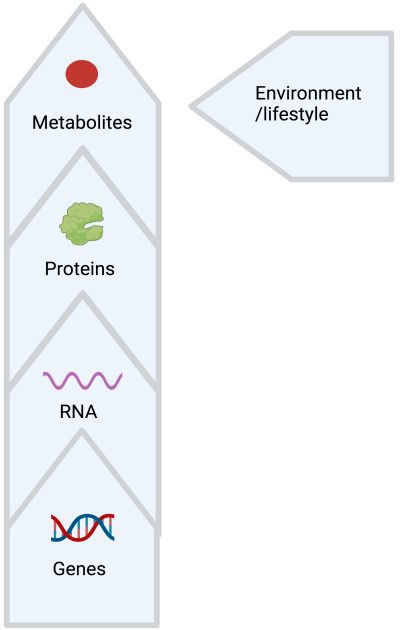

Blood metabolites

- Products of metabolism – life sustaining chemical reactions occurring in your body
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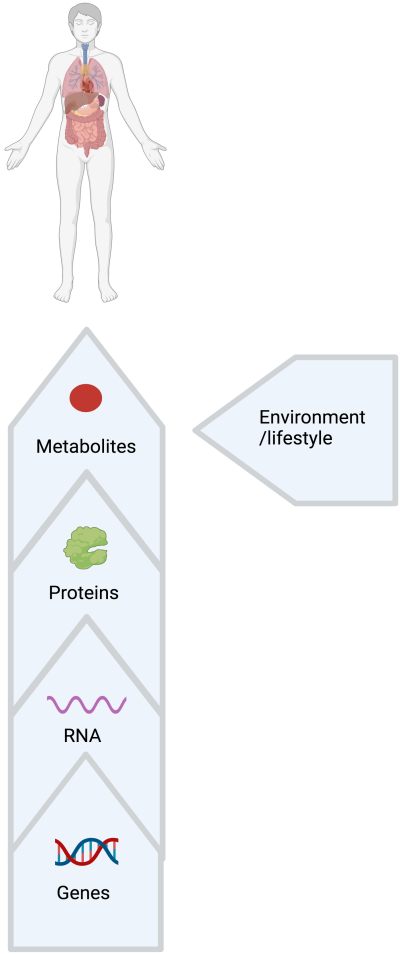
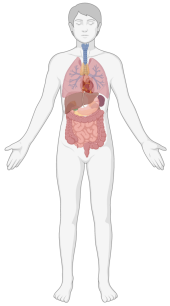
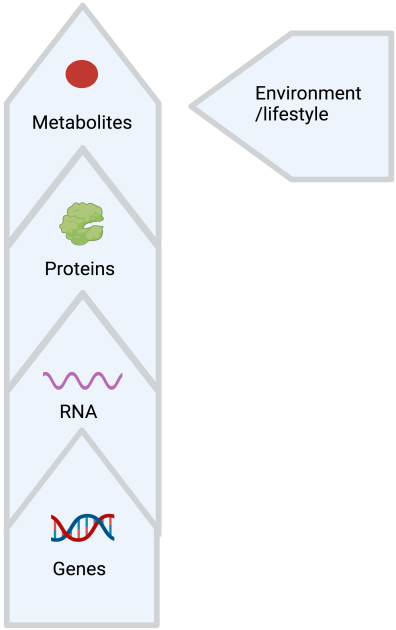
- Real-time snapshot into what is going on in the body



Blood metabolites

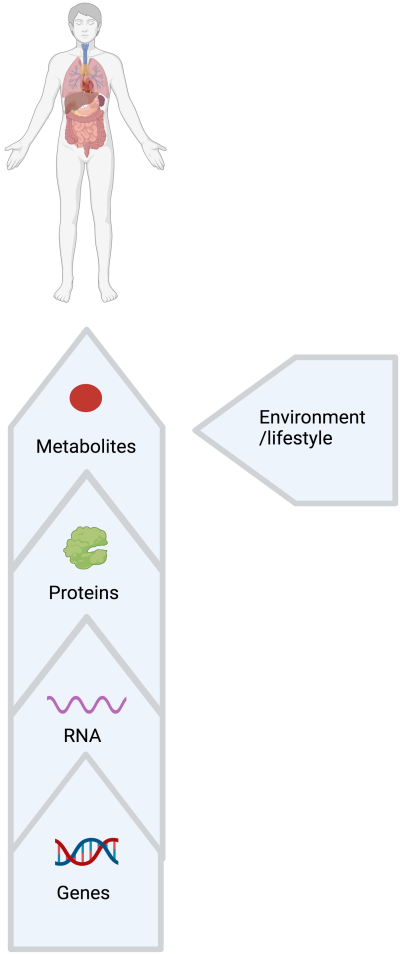
- Products of metabolism – life sustaining chemical reactions occurring in your body
- Small molecules, some can travel into the brain
- Real-time snapshot into what is going on in the body
- Accessible and potentially modifiable





Blood metabolites

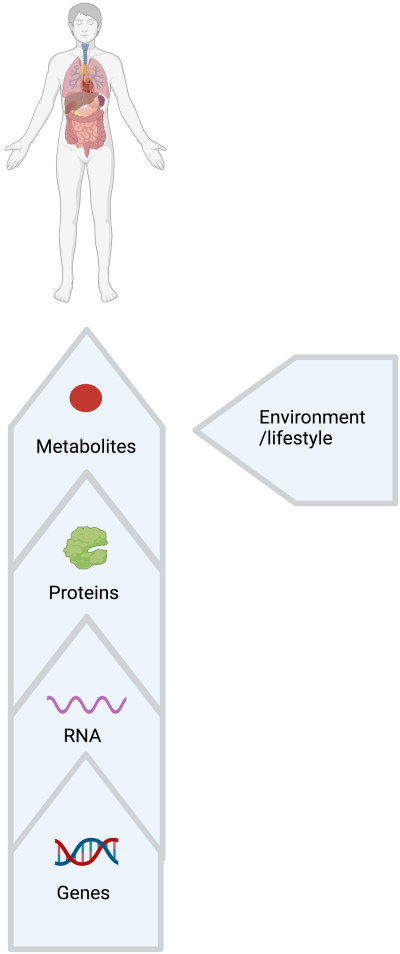
- Products of metabolism – life sustaining chemical reactions occurring in your body
- Small molecules, some can travel into the brain
- Real-time snapshot into what is going on in the body
- Accessible and potentially modifiable
- Relevant



Blood metabolites

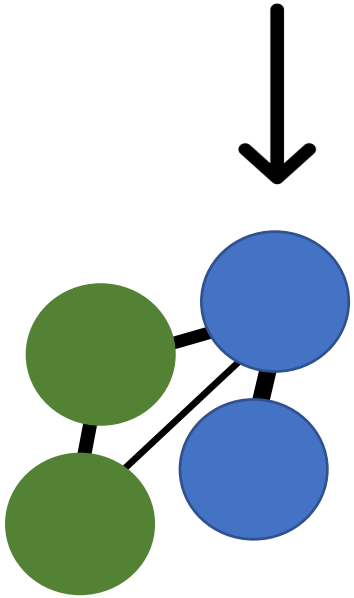
- Products of metabolism – life sustaining chemical reactions occurring in your body
- Small molecules, some can travel into the brain
- Real-time snapshot into what is going on in the body
- Accessible and potentially modifiable
- Relevant

Limitations – clinical or small studies, lifestyle influences, reverse causation, replication



METHIONINE

METHIONINE METABOLISM

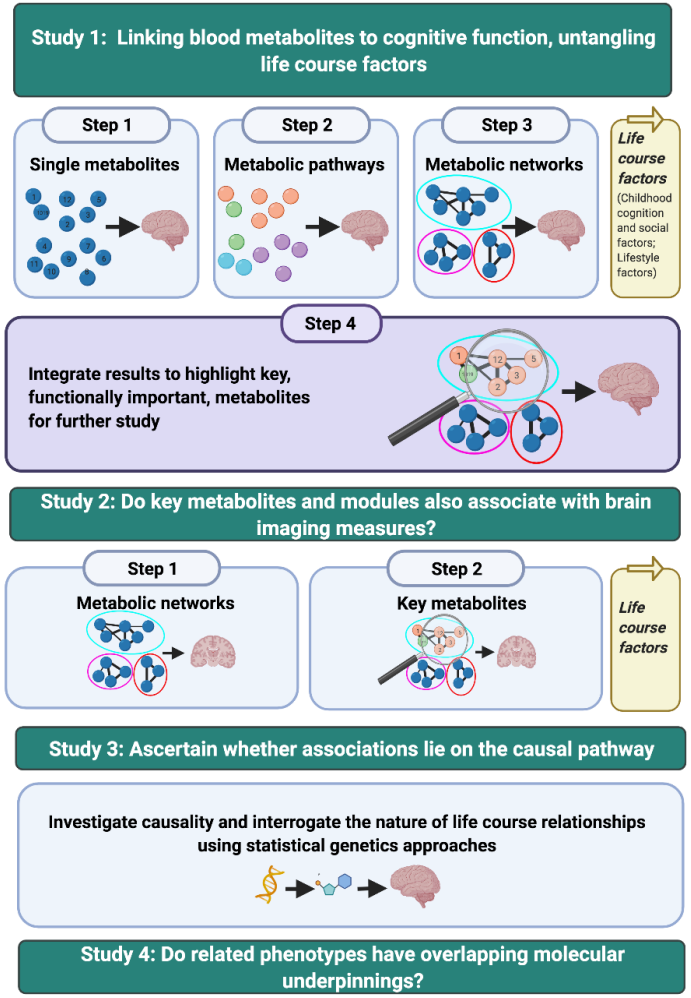


METHIONINE METABOLISM

POLYAMINE METABOLISM

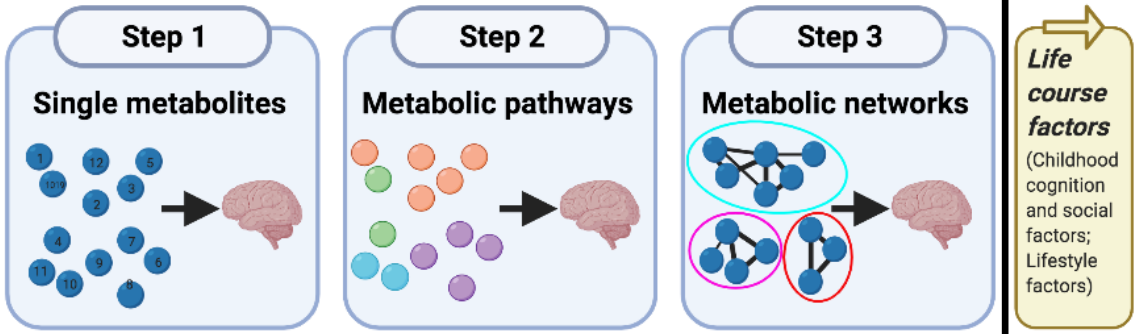
PhD aims

Identify metabolic markers and mechanisms relevant to early dementia, untangling the influence of life course factors

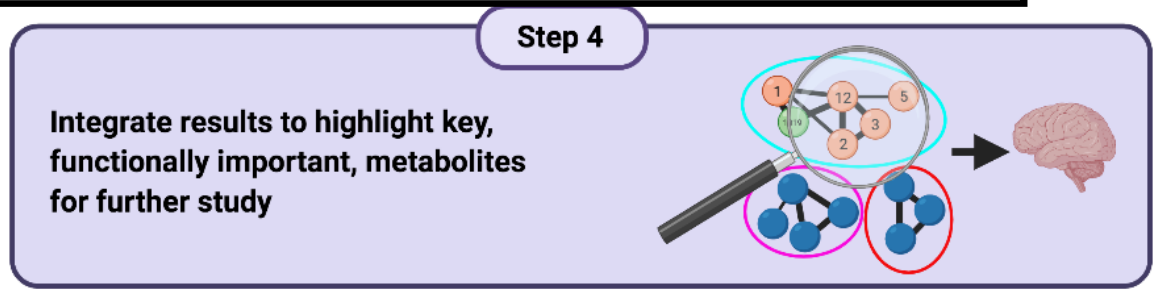

Study 1: Linking blood metabolites to cognitive function, untangling life course factors
Step 1
Single metabolites
Step 2
Metabolic pathways
Step 3
Metabolic networks
Life course factors
(Childhood cognition and social factors; Lifestyle factors)
Step 4
Integrate results to highlight key, functionally important, metabolites for further study
Study 2: Do key metabolites and modules also associate with brain imaging measures?
Step 1
Metabolic networks
Step 2
Key metabolites
Life course factors
Study 3: Ascertain whether associations lie on the causal pathway
Investigate causality and interrogate the nature of life course relationships using statistical genetics approaches
Study 4: Do related phenotypes have overlapping molecular underpinnings?

Study 1: Linking blood metabolites to cognitive function, untangling life course factors

Explore the metabolic underpinnings of cognitive function across the 7th decade of life



Life course factors (Childhood cognition and social factors; Lifestyle factors)

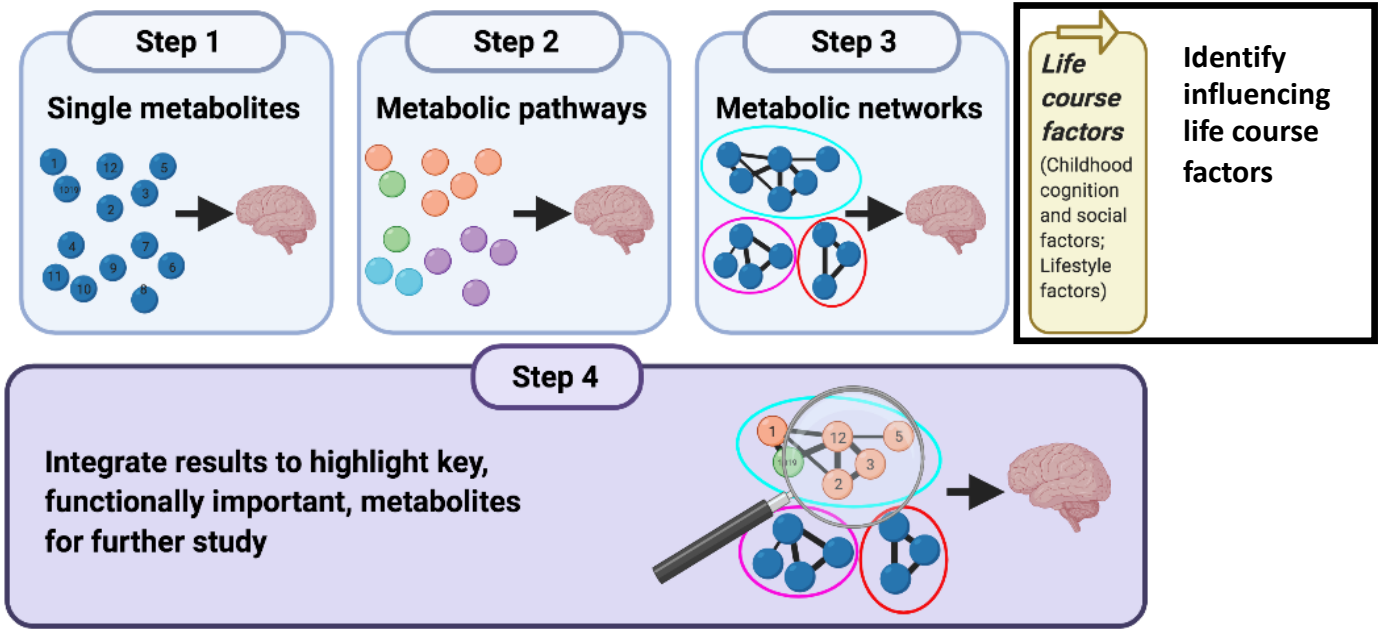


Study 2: Do key metabolites and modules also associate with brain imaging measures?

Green et al., under review

MRC Medical Research Council

Study 1: Linking blood metabolites to cognitive function, untangling life course factors



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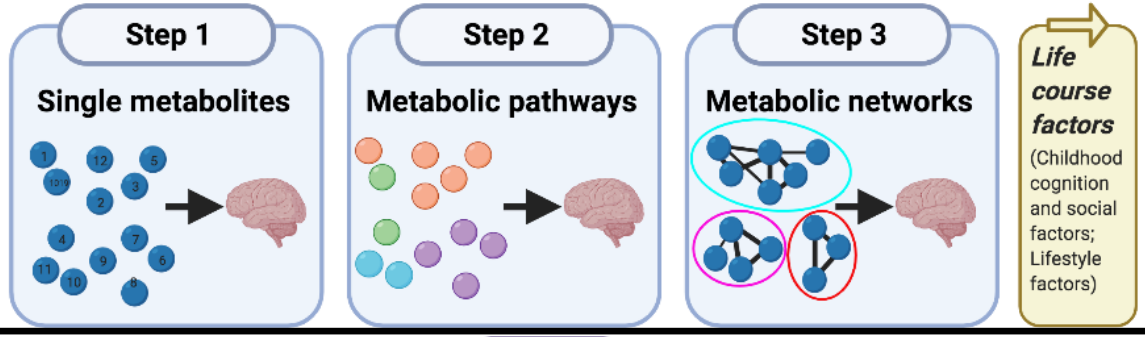
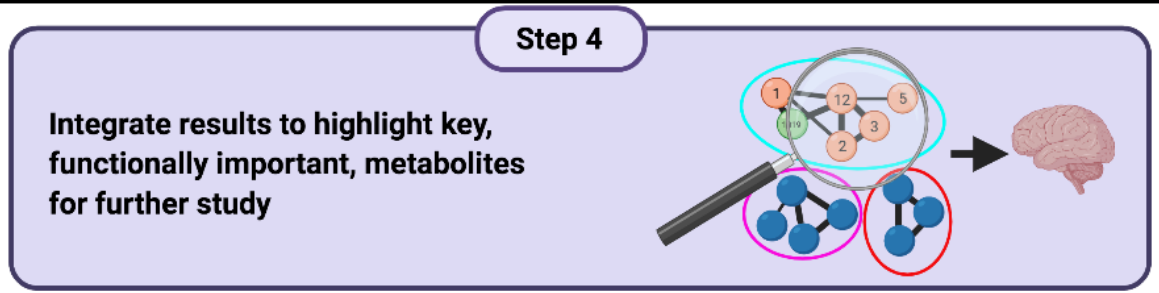


Highlight functionally important metabolites



Study 2: Do key metabolites and modules also associate with brain imaging measures?

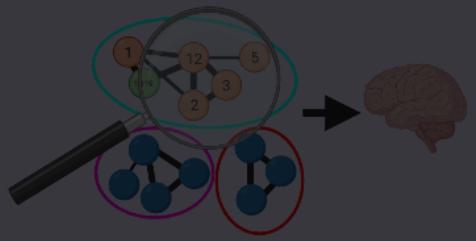
Green et al., under review

Lifestyle factors)

MRC Medical Research Council

Step 4

Integrate results to highlight key, functionally important, metabolites for further study

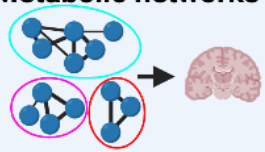


Study 2: Do key metabolites and modules also associate with brain imaging measures?

Identify modules and key metabolites associated with brain imaging measures

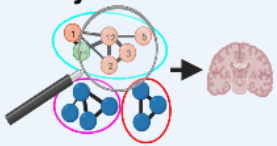
Step 1

Metabolic networks



Step 2

Key metabolites



Life course factors

Study 3: Ascertain whether associations lie on the causal pathway

Investigate causality and interrogate the nature of life course relationships using statistical genetics approaches

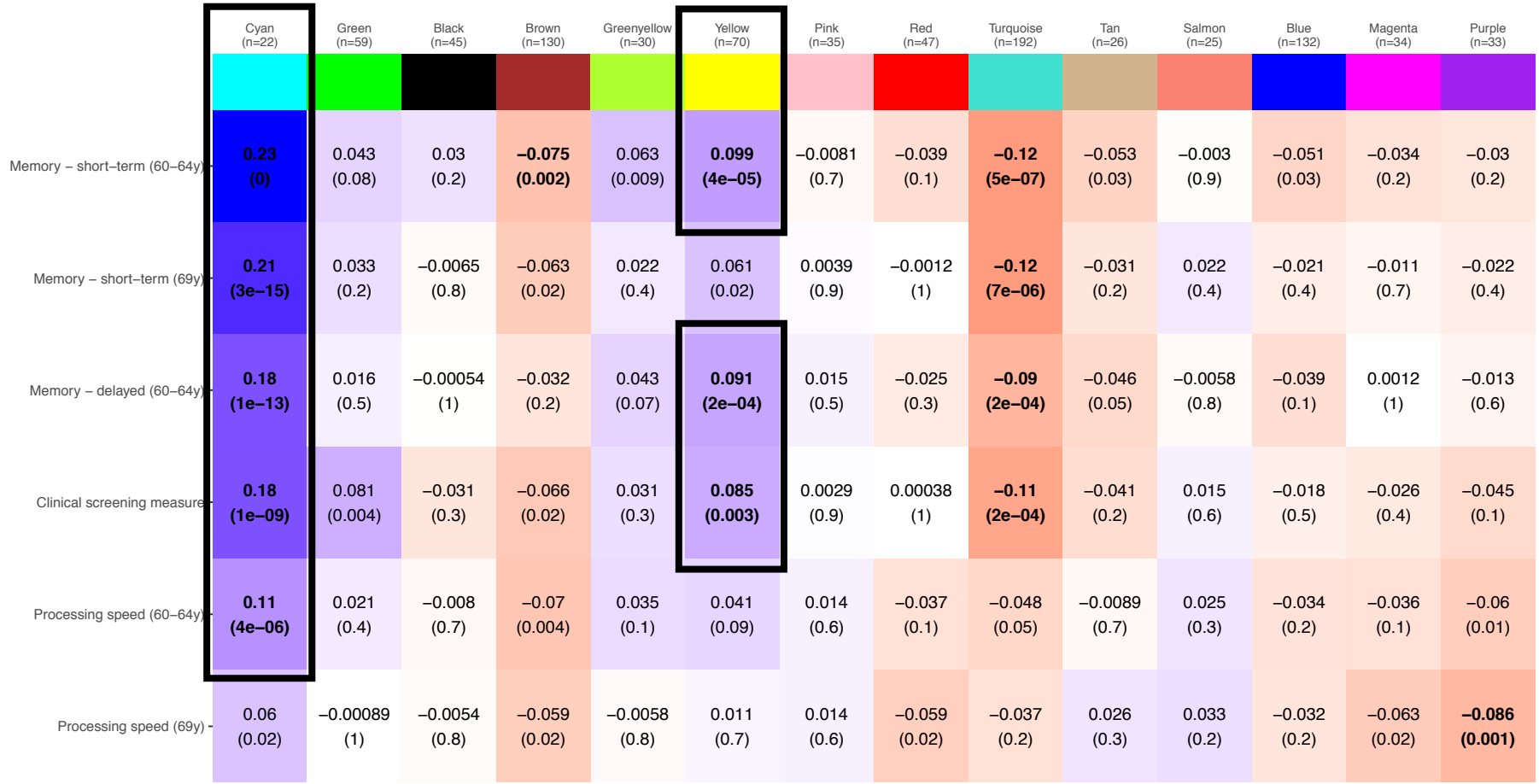
Green et al., under review

Key results (study 1):

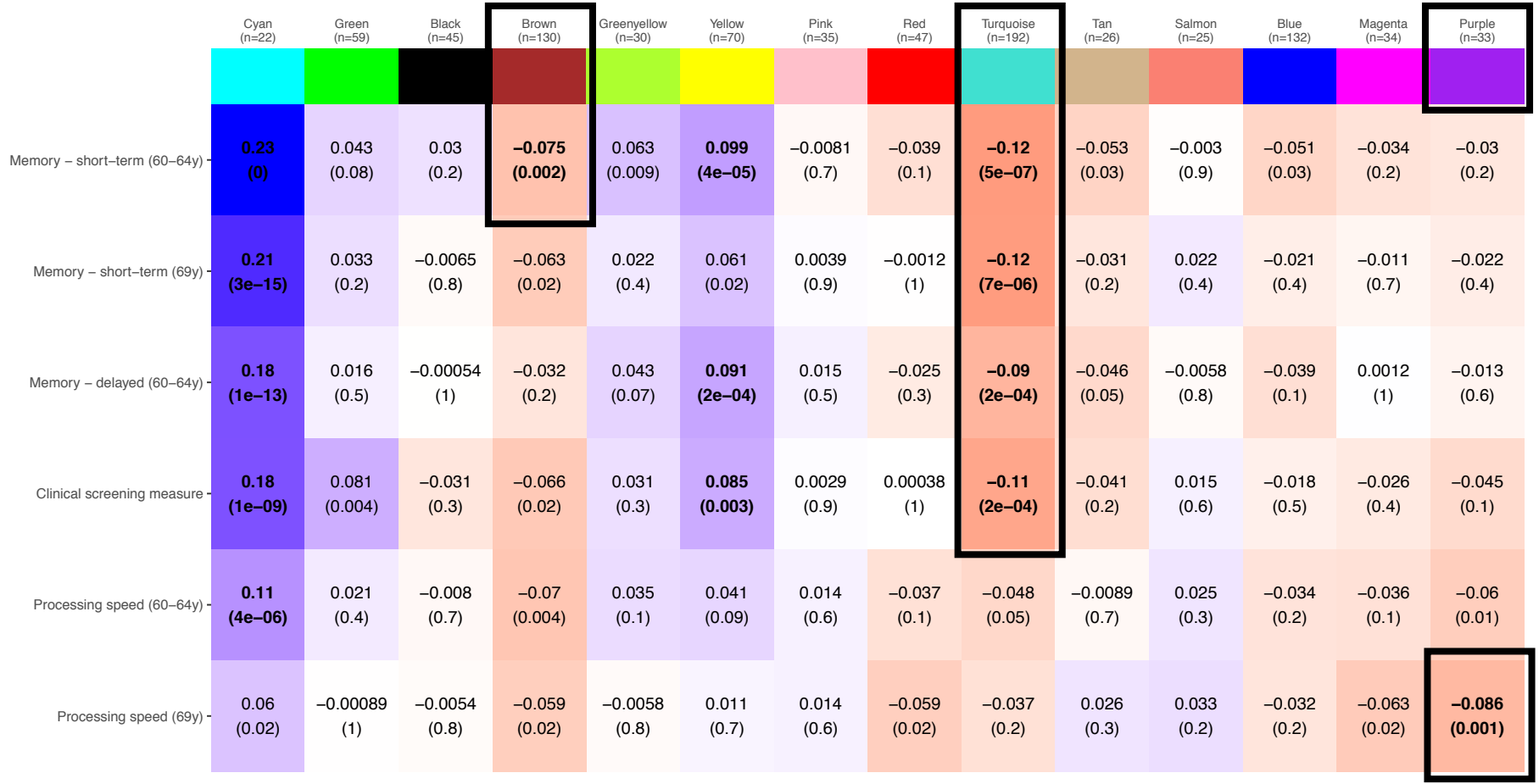
1. **Explore the metabolic underpinnings of aspects of cognitive function across the 7th decade of life**

   - 155 metabolites, 10 pathways, 5 network modules
   - Some associations unique to particular cognitive domains
   - 28 key metabolites belonging to the 5 modules

Green et al., under review



Green et al., under review



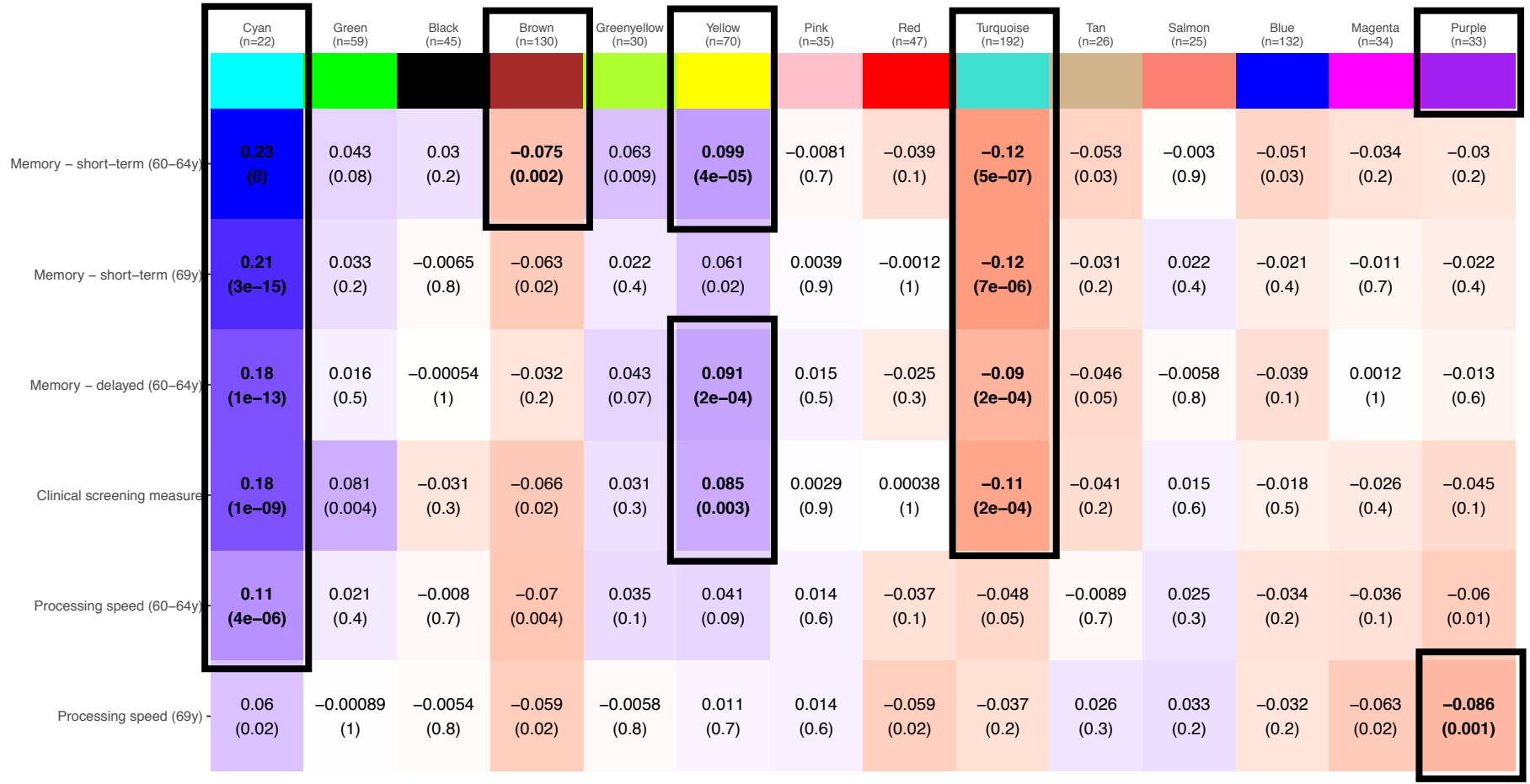
Green et al., under review

Key results (study 1):

2. Untangle influencing life course factors

- Many sensitive to earlier life cognitive and social factors, particularly childhood cognition
- Some independent relationships

Green et al., under review



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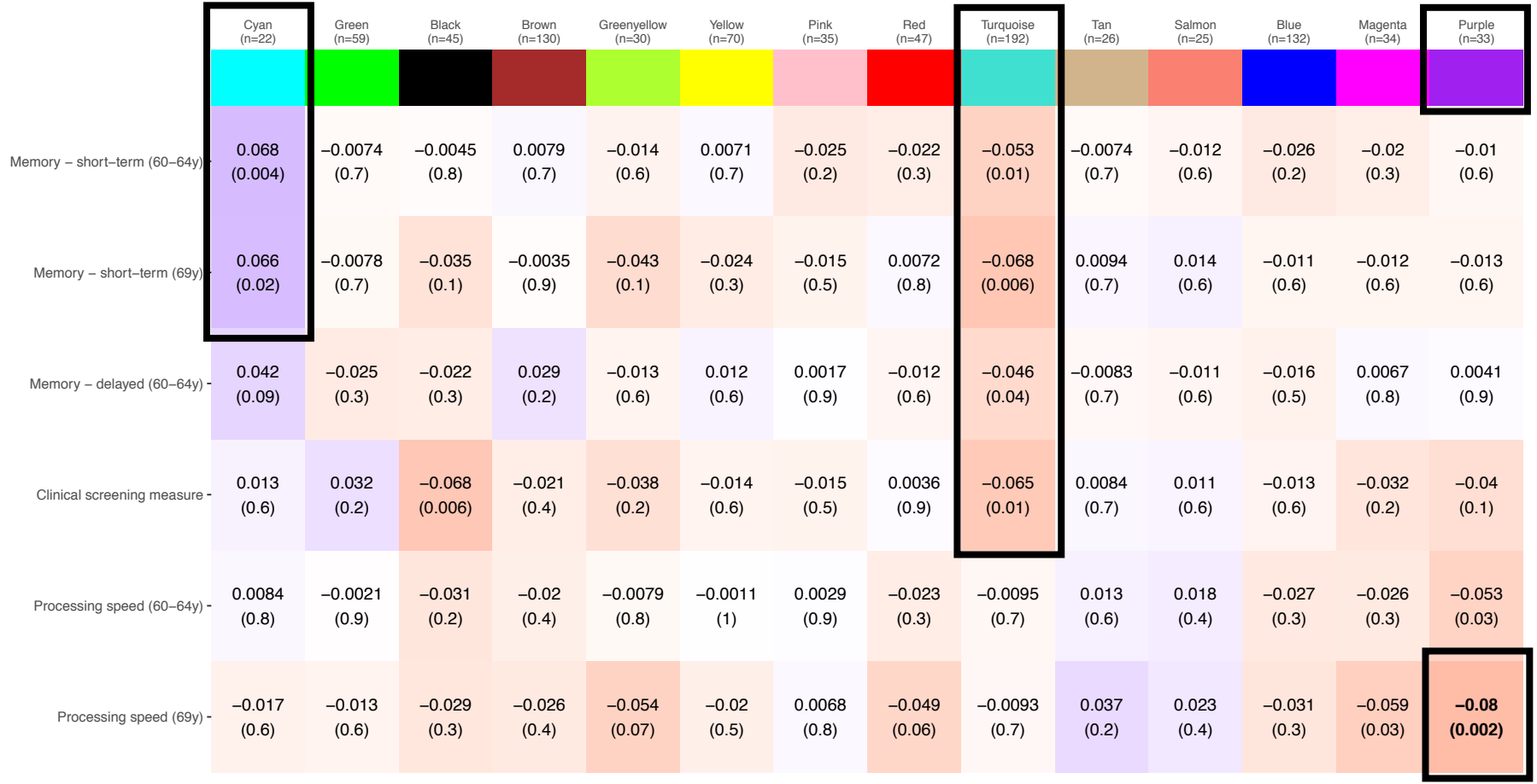

Green et al., under review

What about brain imaging? (study 2)

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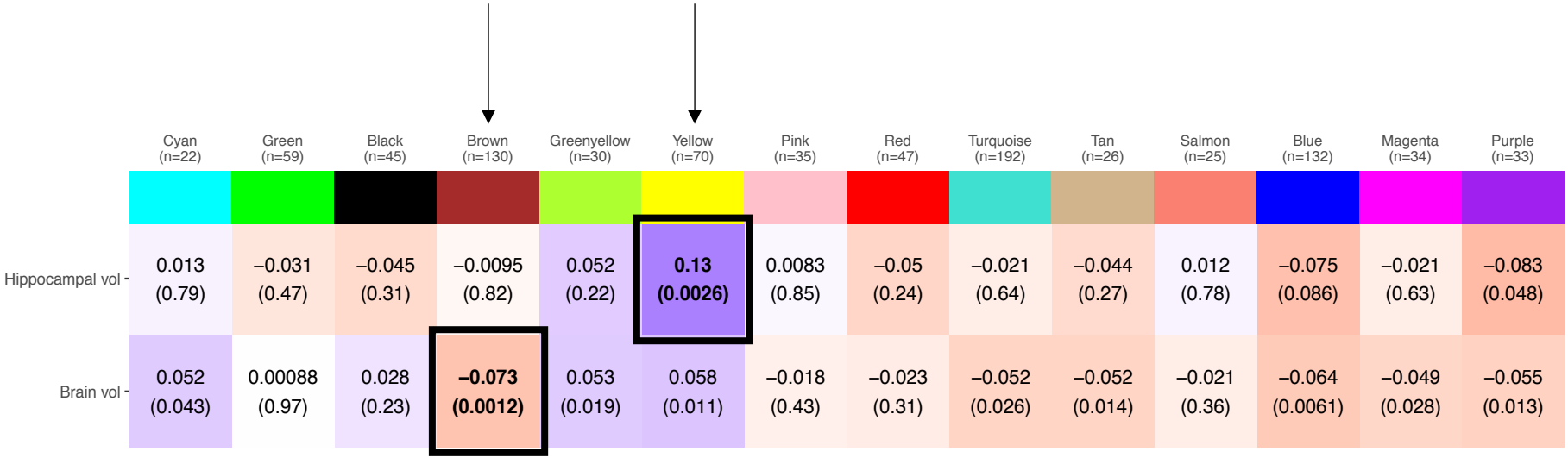
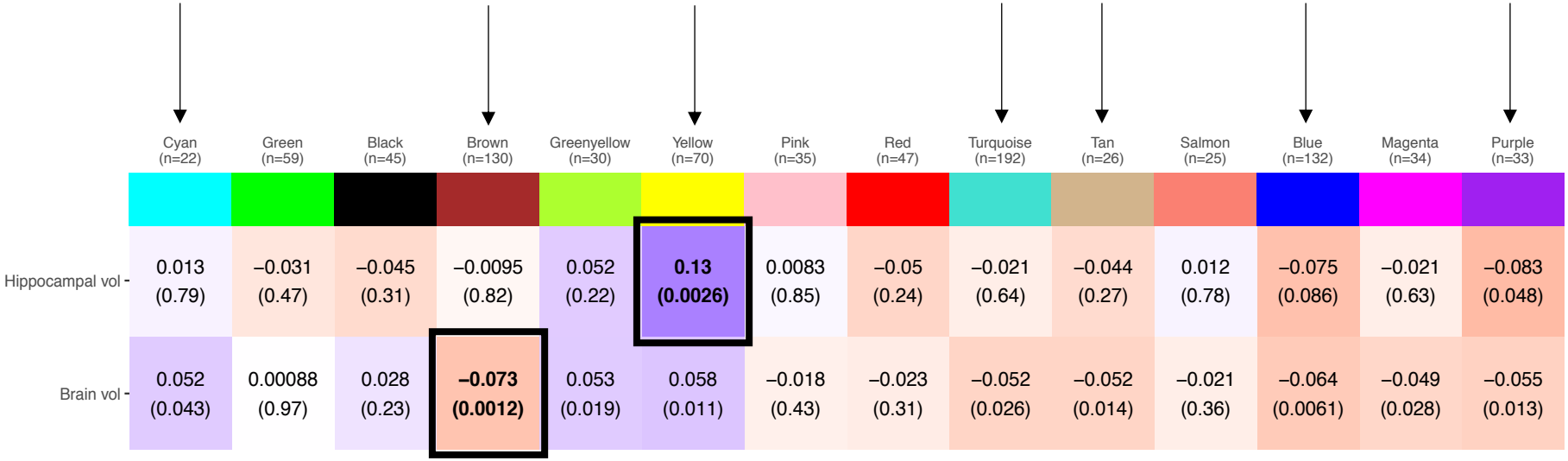


Yellow (hippocampal volume), brown (whole brain volume)

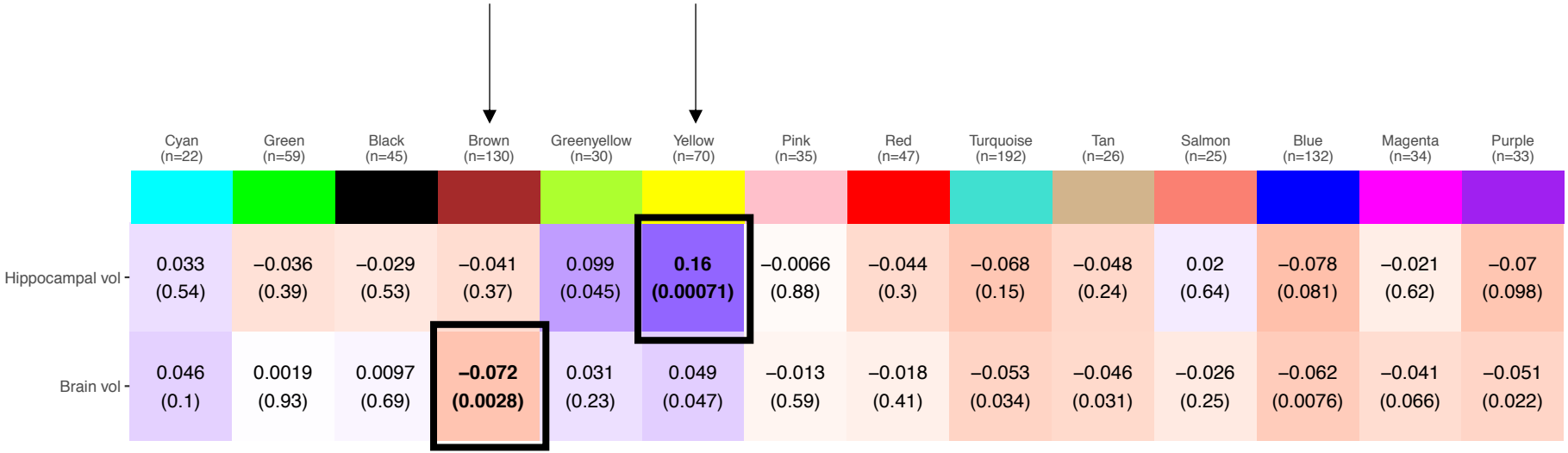
What about brain imaging? (study 2)



5/5 showed nominal associations + 2 additional for whole brain volume

12 of the key metabolites + some extra identified

What about brain imaging? (study 2)



Associations persisted after adjusting for life course factors

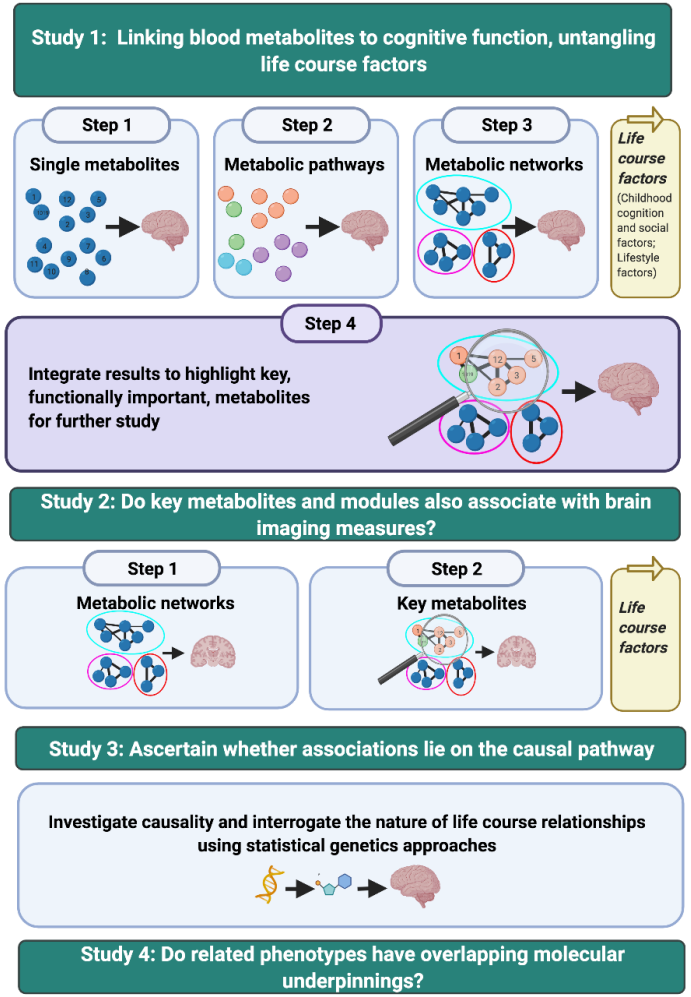
Summary

- Metabolic mechanisms highlighted:
- Role of particular fatty acids in processing speed; role of vitamin A/C metabolites and modified nucleosides and amino acids in memory (part explained by life course factors)
- Role of sphingolipid metabolism in hippocampal volume, phospholipids in whole brain volume

- 30 key metabolites - marker candidates?

- Life course factors - reverse causation, other confounding?

Future directions

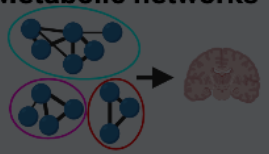


functionally important, metabolites for further study

Study 2: Do key metabolites and modules also associate with brain imaging measures?

Step 1

Metabolic networks



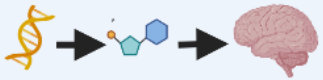
Step 2

Key metabolites

Life course factors

Study 3: Ascertain whether associations lie on the causal pathway

Investigate causality and interrogate the nature of life course relationships using statistical genetics approaches



Study 4: Do related phenotypes have overlapping molecular underpinnings?

Thank you!

Thank you to my supervisors and coauthors who make this work possible:

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Min Kim
Jane Maddock
Andy Wong
Cristina Legido-Quigley
Richard Dobson
SGU Team

Twitter: @becki_e_green

Email: rebecca.e.green@kcl.ac.uk

Website: beckigreen.netlify.app

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