LINKING BLOOD METABOLITES TO EARLY CHANGES RELEVANT TO DEMENTIA: FINDINGS FROM THE MRC 1946 BRITISH BIRTH COHORT

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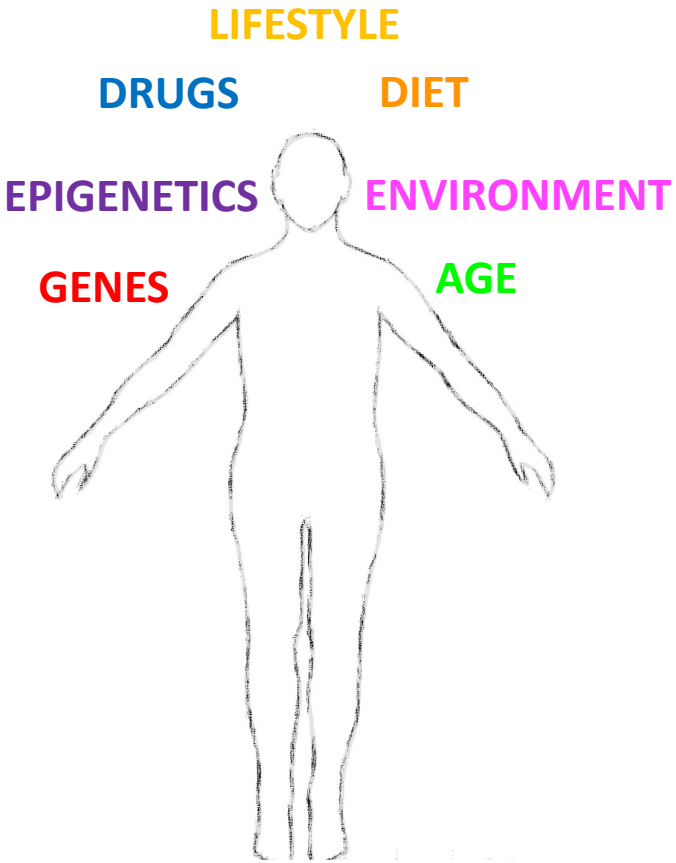
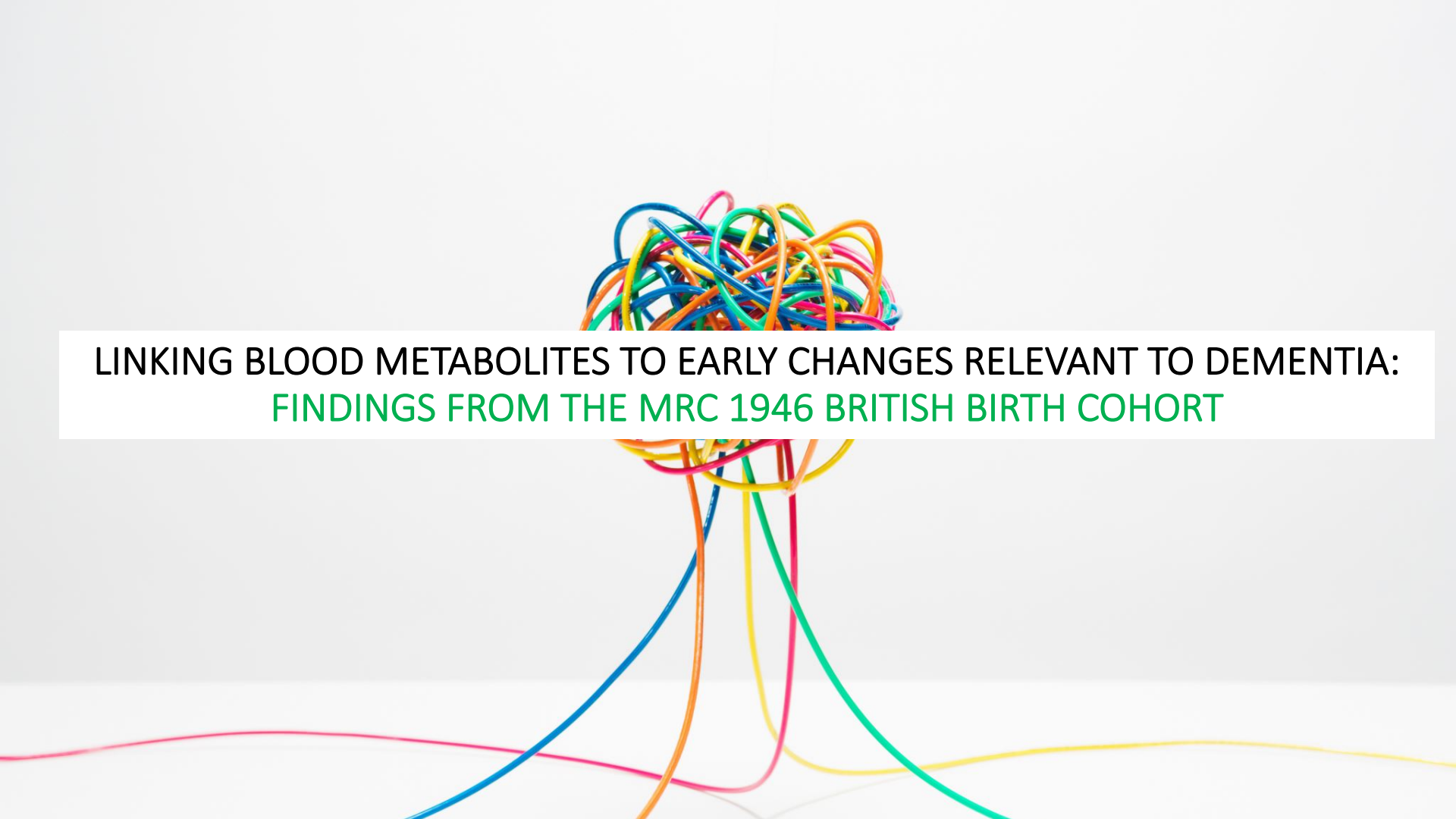
Why blood metabolites?

- Metabolites = small molecules, intermediates/end products of biological events
- Metabolome = the body's metabolic make up
- Holistic – capture influences of genetics as well as environment and lifestyle
- Accessible and potentially modifiable - marker?
- Relevant – brain lipid rich, previously linked to cognitive function and AD
- Levels influenced by external factors (e.g. lifestyle, environment) which are rarely accounted for



Why early changes relevant to dementia?

- Long prodrome, lifelong influences?
- Little is known about early mechanisms
- Early markers – great opportunity to prevent or delay pathology
- Late midlife cognitive function – key predictor



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The MRC 1946 British Birth Cohort Study

- World's longest continually running birth cohort
- 5362 participants born in March 1946 - LC-MS metabolomics data (N=1800), Insight46 (neuroimaging) (N=500)
- Deeply phenotyped
- Broadly representative of the population in mainland Britain at that time
- Key age

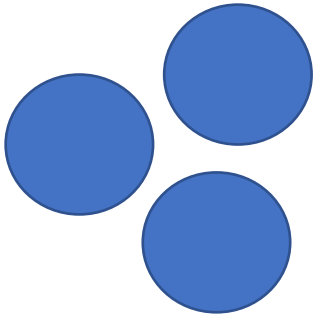
Study aims:

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

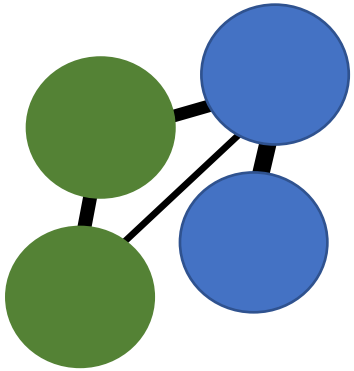
2. Untangle influencing life course factors

<u>Highlight potential mechanisms and markers of cognitive outcomes in this key age period</u>

METHIONINE

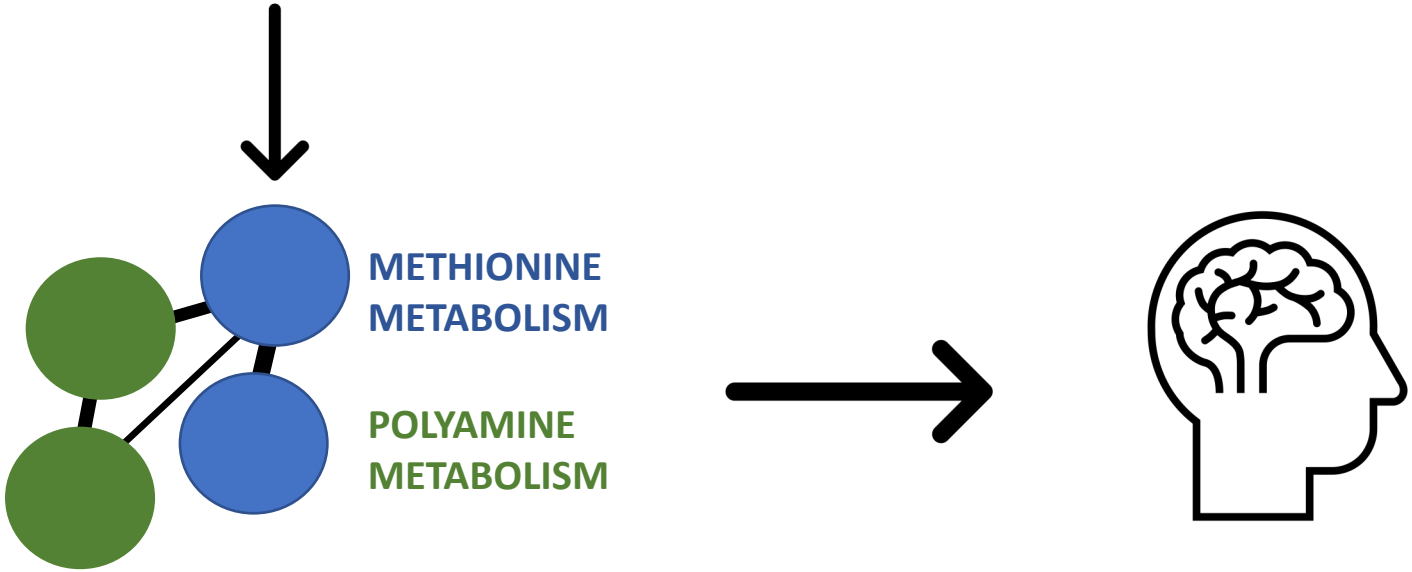


METHIONINE METABOLISM



METHIONINE METABOLISM

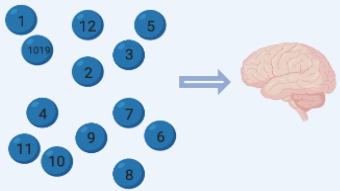
POLYAMINE METABOLISM


METHIONINE
METABOLISM
POLYAMINE
METABOLISM

MRC 1946 British Birth Cohort Study (n=1740)

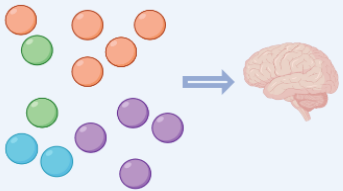
Step 1

Identify single metabolites associated with cognitive outcomes at baseline and 5-9 years later



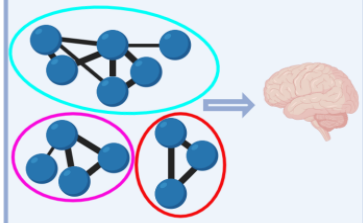
Step 2

Identify metabolite pathways associated with cognitive outcomes at baseline and 5-9 years later

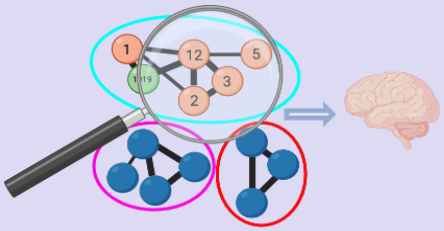


Step 3

Identify metabolite modules associated with cognitive outcomes at baseline and 5-9 years later



Step 4 - Integrate results to reveal key drivers and pathways

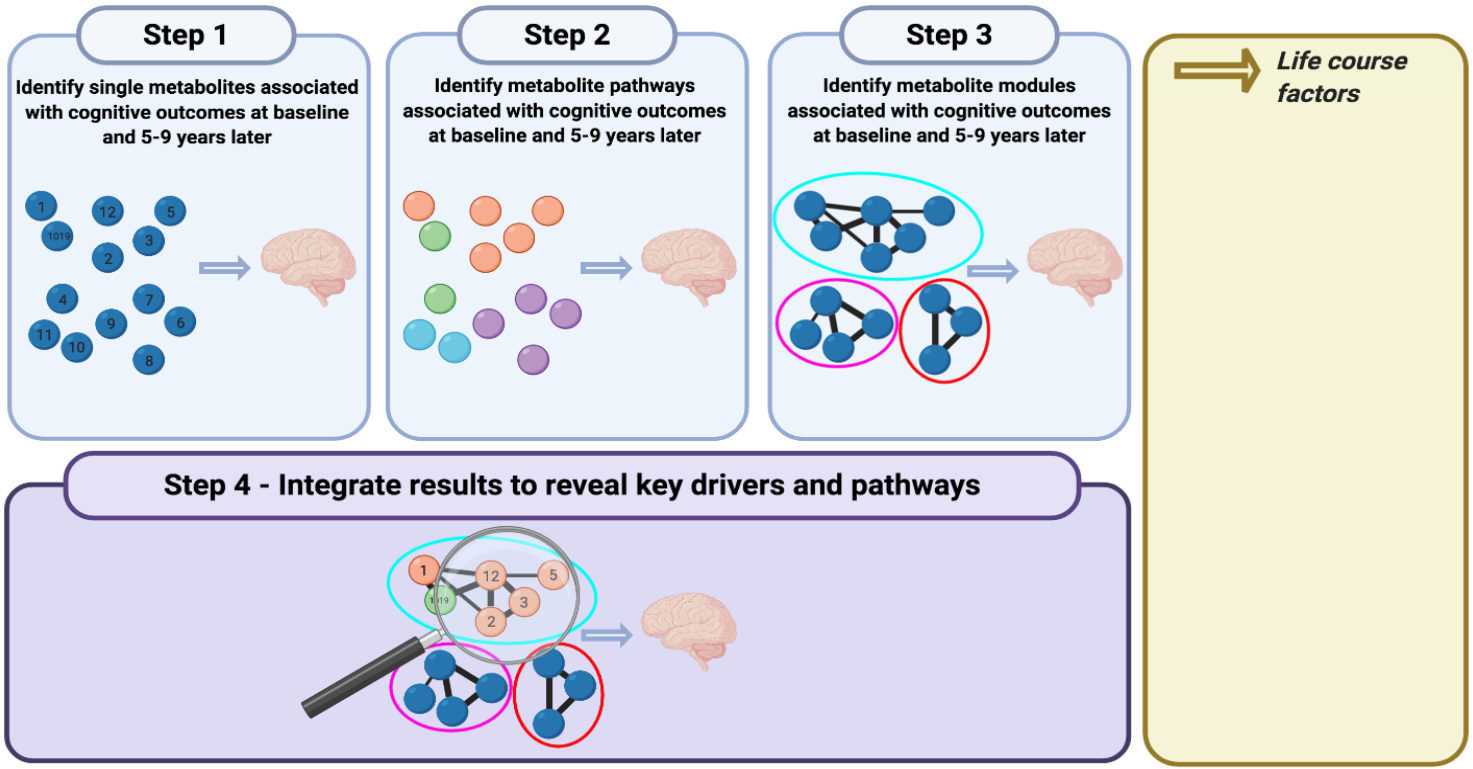


Life course factors

- Lipid medication
- BMI
- Childhood cognition
- Education
- SEP
- Exercise
- Blood pressure
- Smoking
- Alcohol
- Diet

Green et al., in preparation

MRC 1946 British Birth Cohort Study (n=1740)



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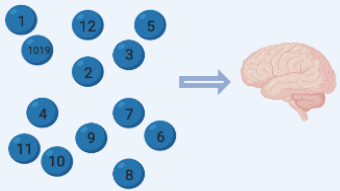

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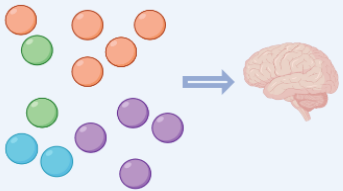

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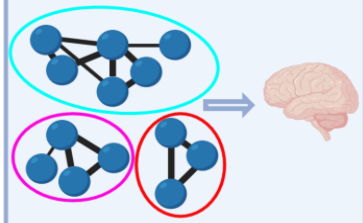
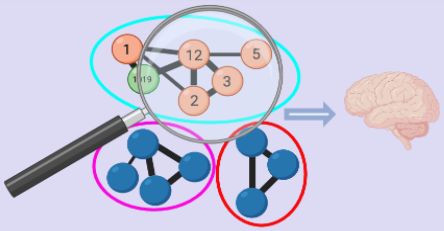


Step 4 - Integrate results to reveal key drivers and pathways



Life course factors

Lipid medication

BMI

MODEL 2
(Classic metabolite confounders)

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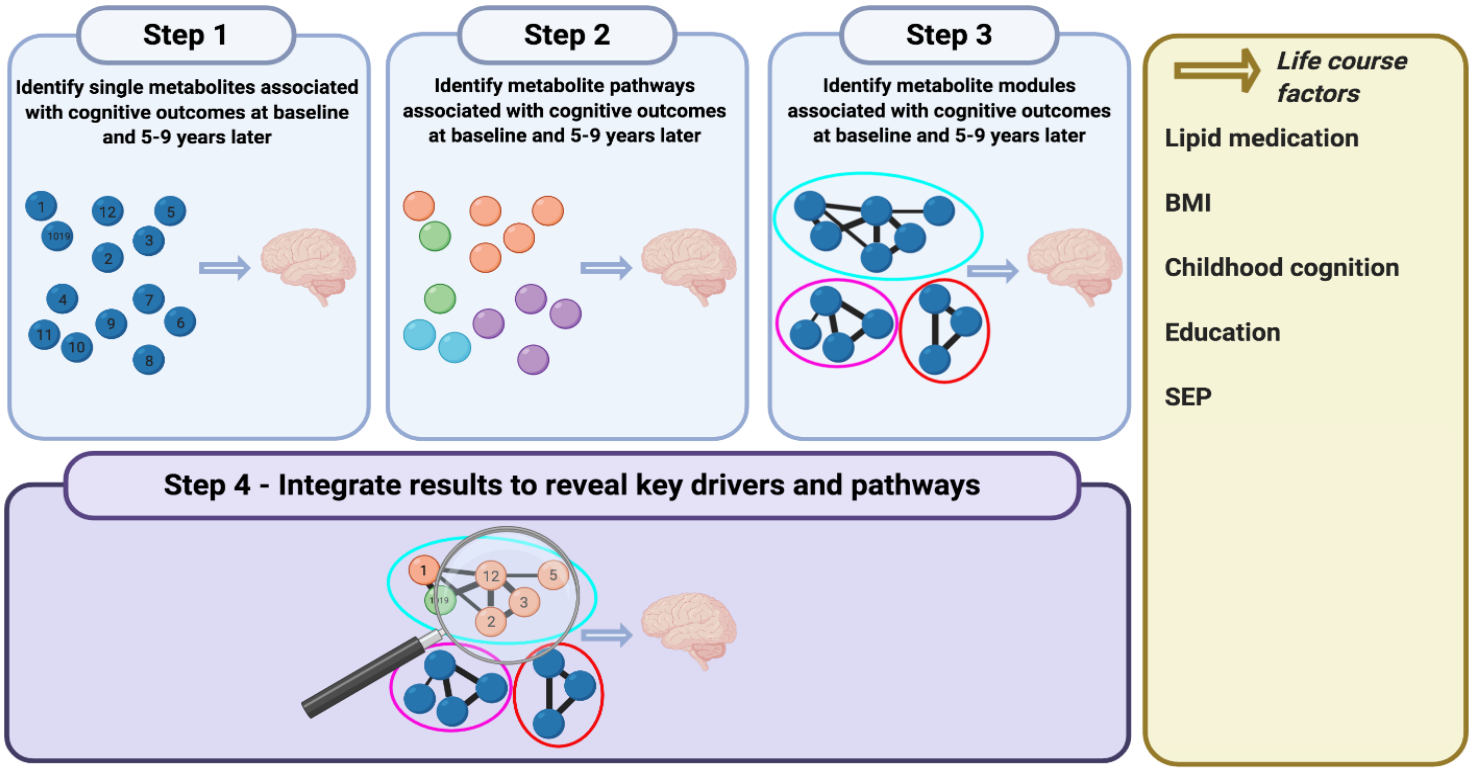
MRC 1946 British Birth Cohort Study (n=1740)



MODEL 3
(Earlier life cognitive and social factors)

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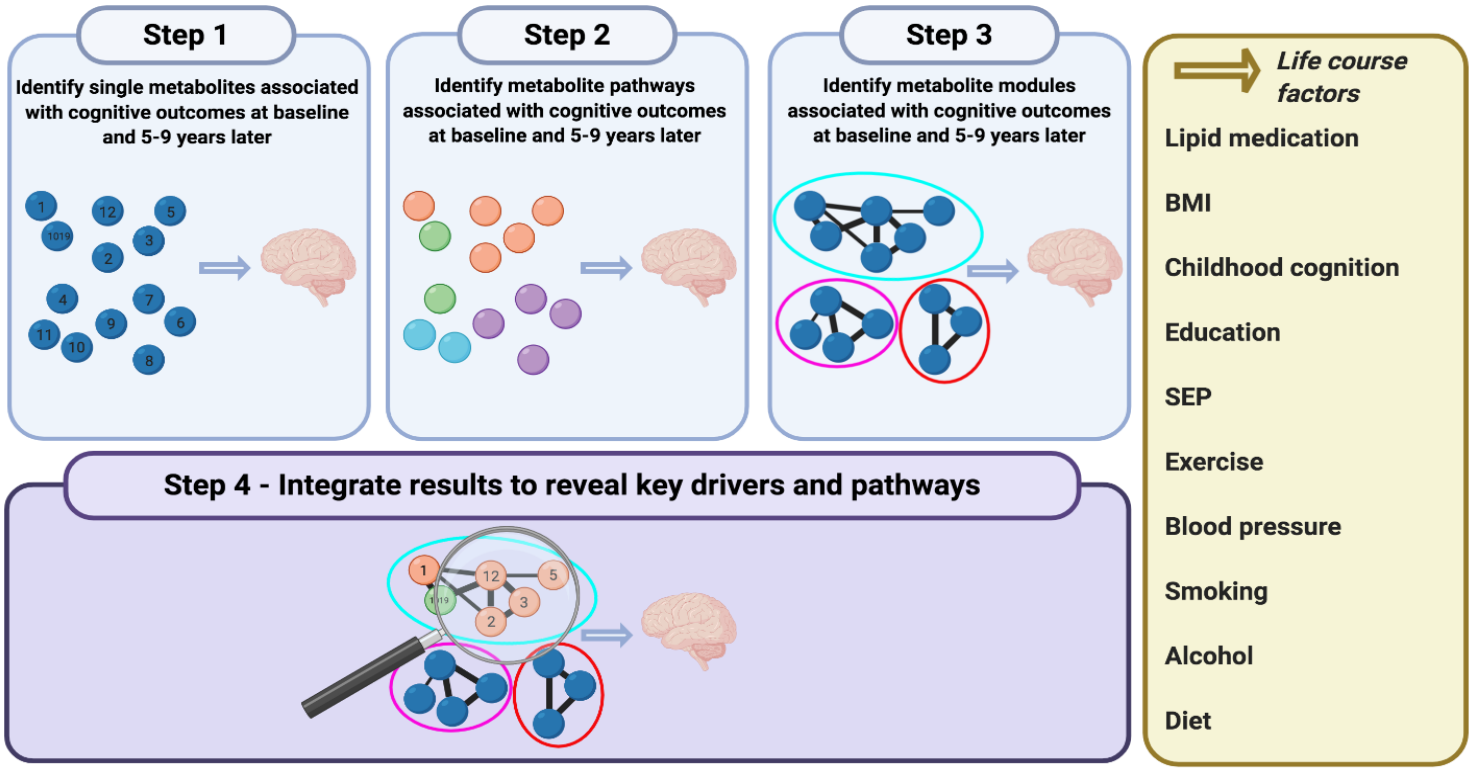
MRC 1946 British Birth Cohort Study (n=1740)



MODEL 4
(Lifestyle factors)

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Key results:

1. **Explore the metabolic correlates of aspects of cognitive function across the 7th decade of life**
   - 155 metabolites, 10 pathways, 5 modules
   - Results complimentary through multiple analytical designs
   - 35 key drivers for further study
   - Some associations unique to particular cognitive domains

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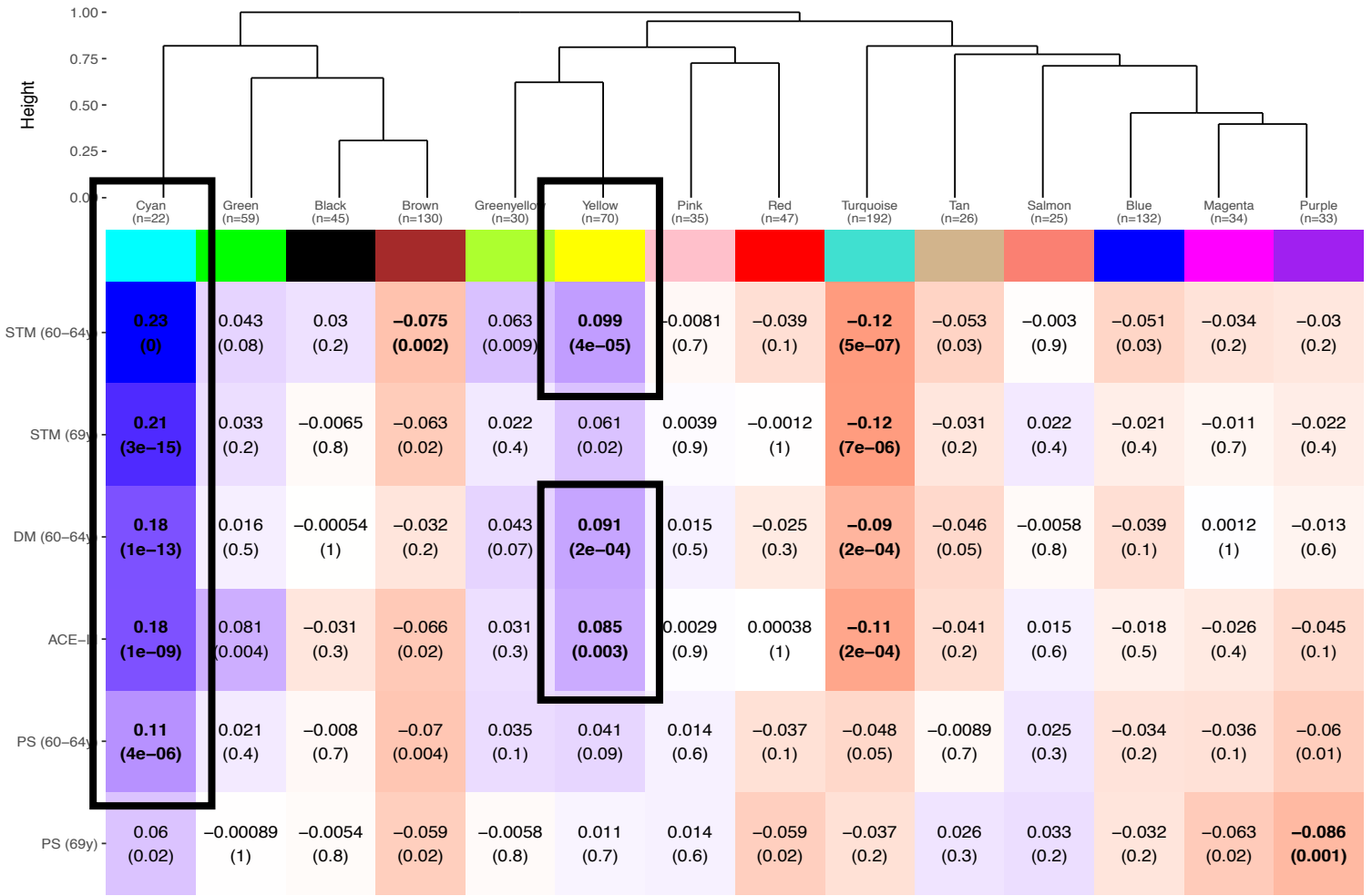

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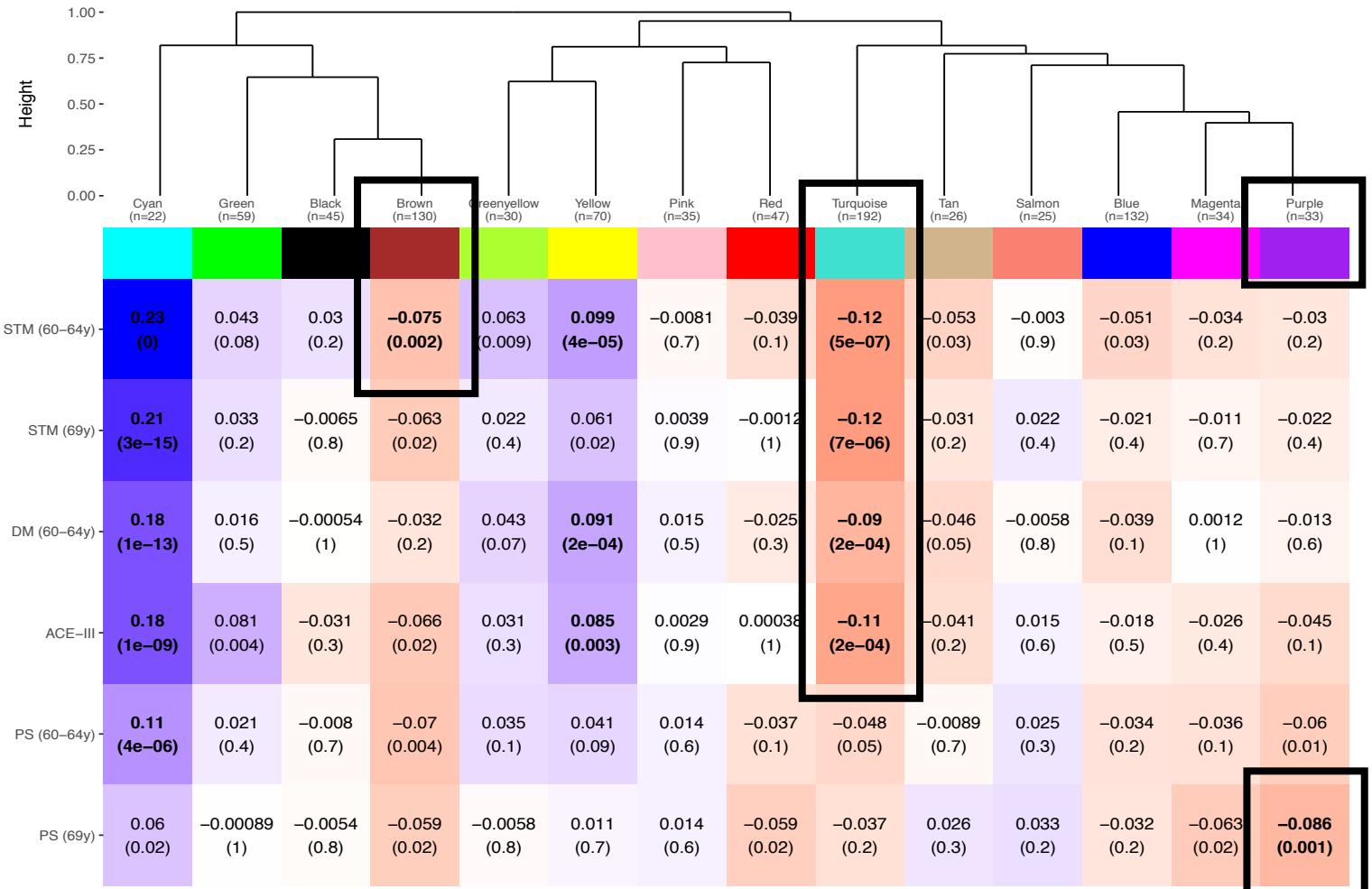

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Key results:

2. **Untangle influencing life course factors**
   - Mostly sensitive to earlier life cognitive and social factors, particularly childhood cognition and education
   - Some independent relationships

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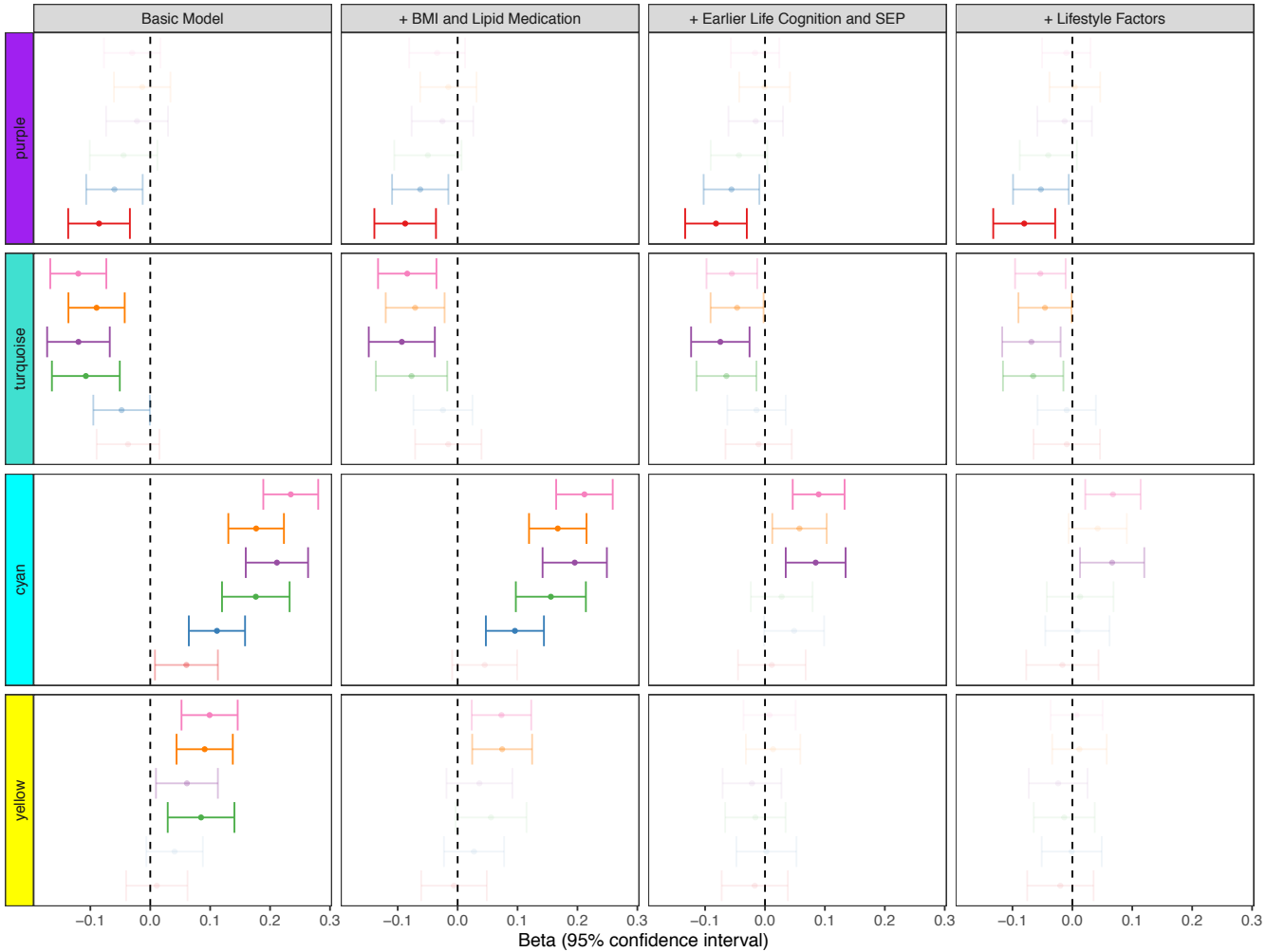
Negative relationships between module of medium and long chain acylcarnitines (purple), independent of life course factors



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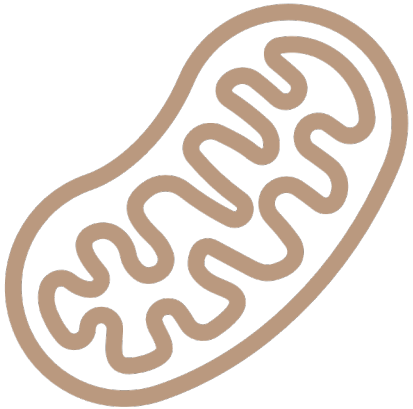
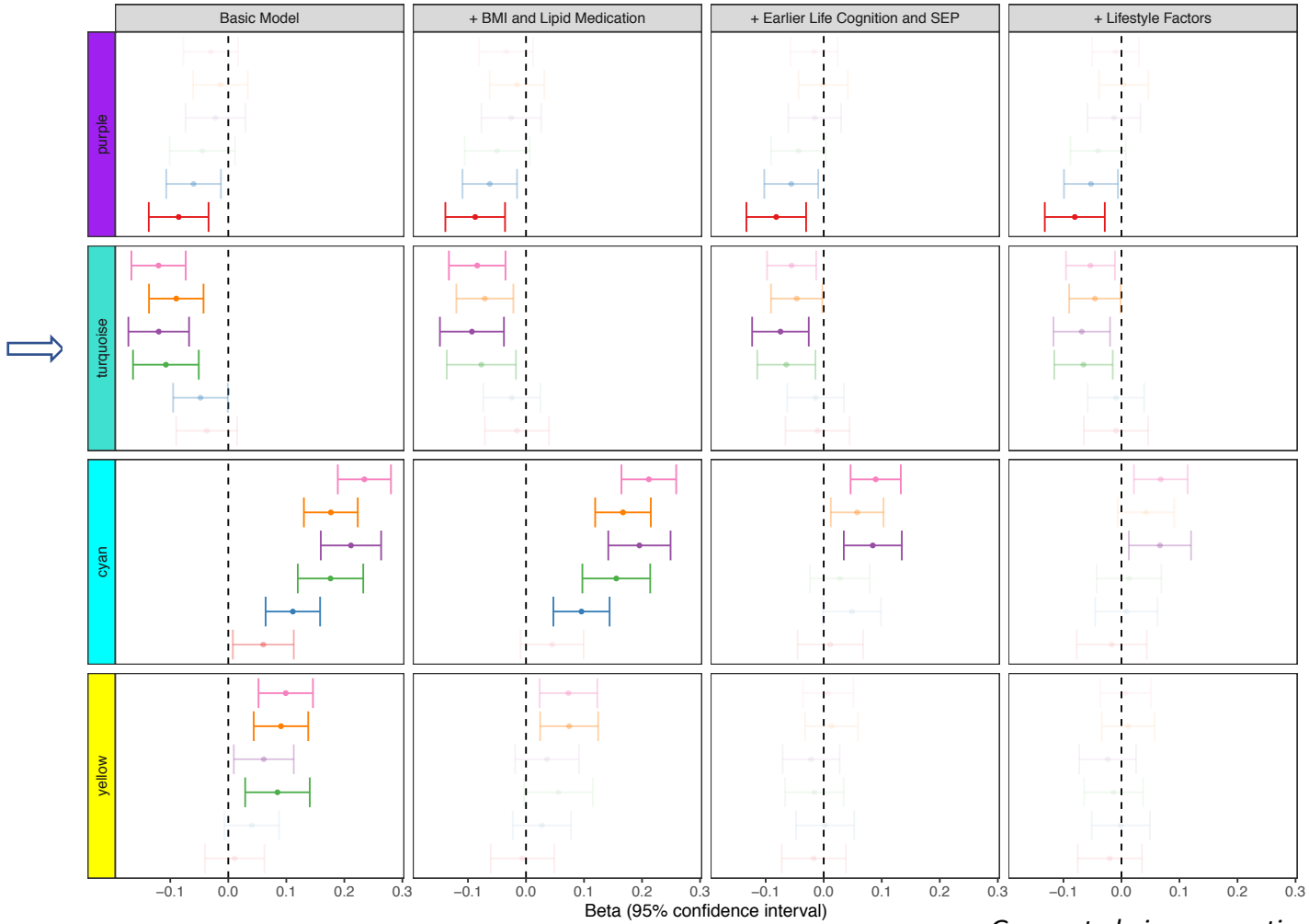
Medium and long chain acylcarnitines

- Derivatives of fatty acid metabolism
- Pivotal in mitochondrial fatty acid oxidation
- Proxy for mitochondrial dysfunction and impairments in energy production?
- Potential mechanism underlying worse processing speed
- Palmitoylcarnitine – marker candidate?



Negative relationships between module comprised of modified amino acids and nucleosides (turquoise), partly attenuated by life course factors



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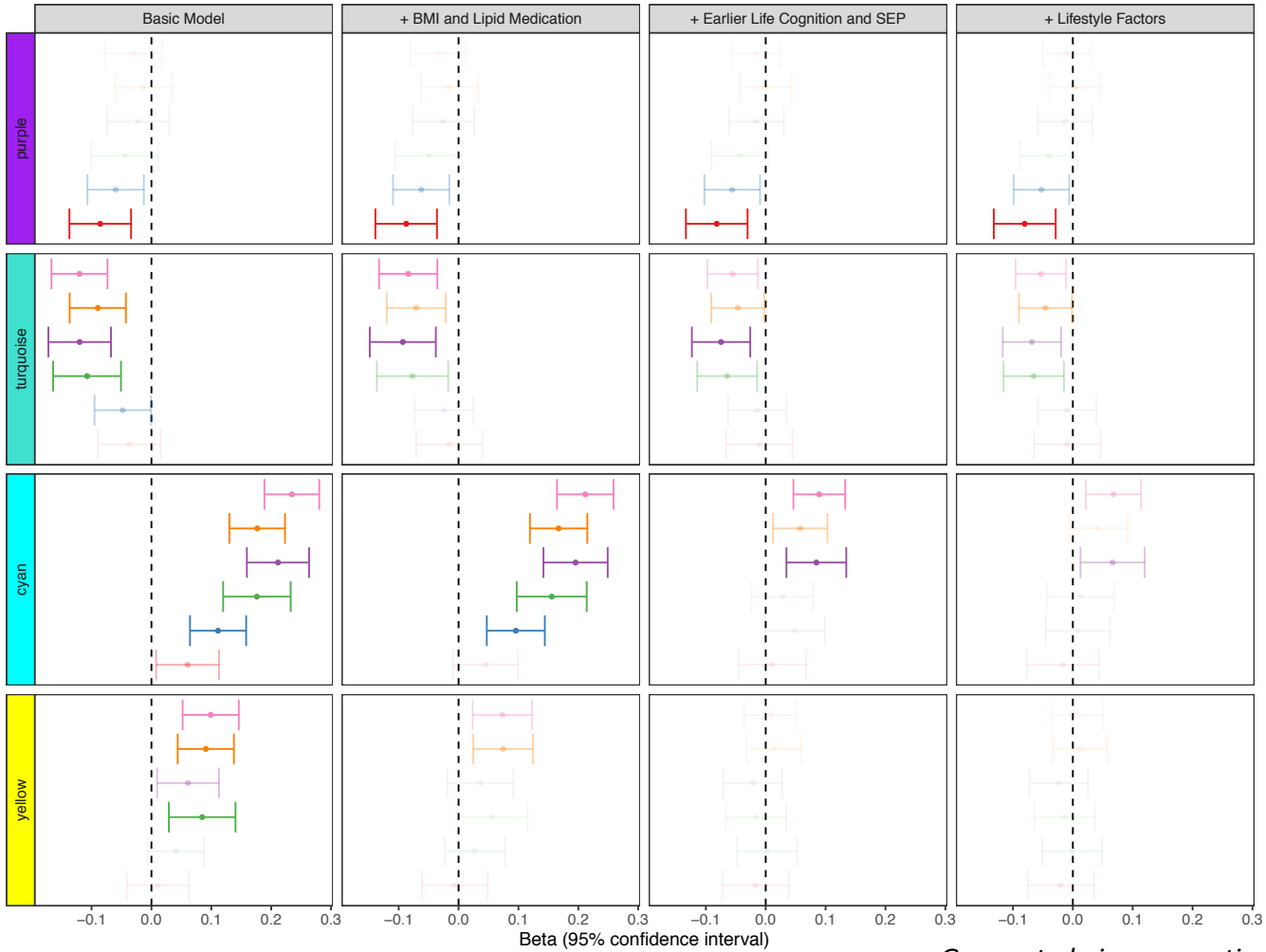
Modified nucleosides and amino acids

- Particular “signature” of metabolites linked to a whole host of adverse health outcomes
- Related factors unable to suitably explain relationships
- Likened to an accelerated ageing phenotype
- Marker of tissue breakdown and oxidative stress?

Positive relationships between module comprised of vitamin A and C metabolites (cyan) and sphingolipids (yellow), fully or partly attenuated by life course factors



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What about associations that attenuate?

- Childhood cognition & education – common confounders
- Perhaps capturing earlier relationships?
- BMI – confounder/mediator?
- Important to unpick this further

FUTURE DIRECTIONS

Largest metabolomics study to date on cognitive function

Used a comprehensive design, illuminating mechanisms and marker candidates for further investigation

Accounting for life course factors identified independent associations and considerations for future studies

Do these metabolites lie on the causal pathway? What do these life course relationships mean?

What about neuroimaging outcomes?

Thank you!

Thank you to my supervisors and coauthors who make this work possible:
Petra Proitsi
Marcus Richards
Jodie Lord
Jin Xu
Min Kim
Jane Maddock
Andy Wong
Cristina Legido-Quigley
Richard Dobson
SGDP Centre colleagues

Funders

MRC Medical Research Council

NIHR | Maudsley Biomedical Research Centre

A special thanks to all MRC 1946 study members for their lifelong participation.

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