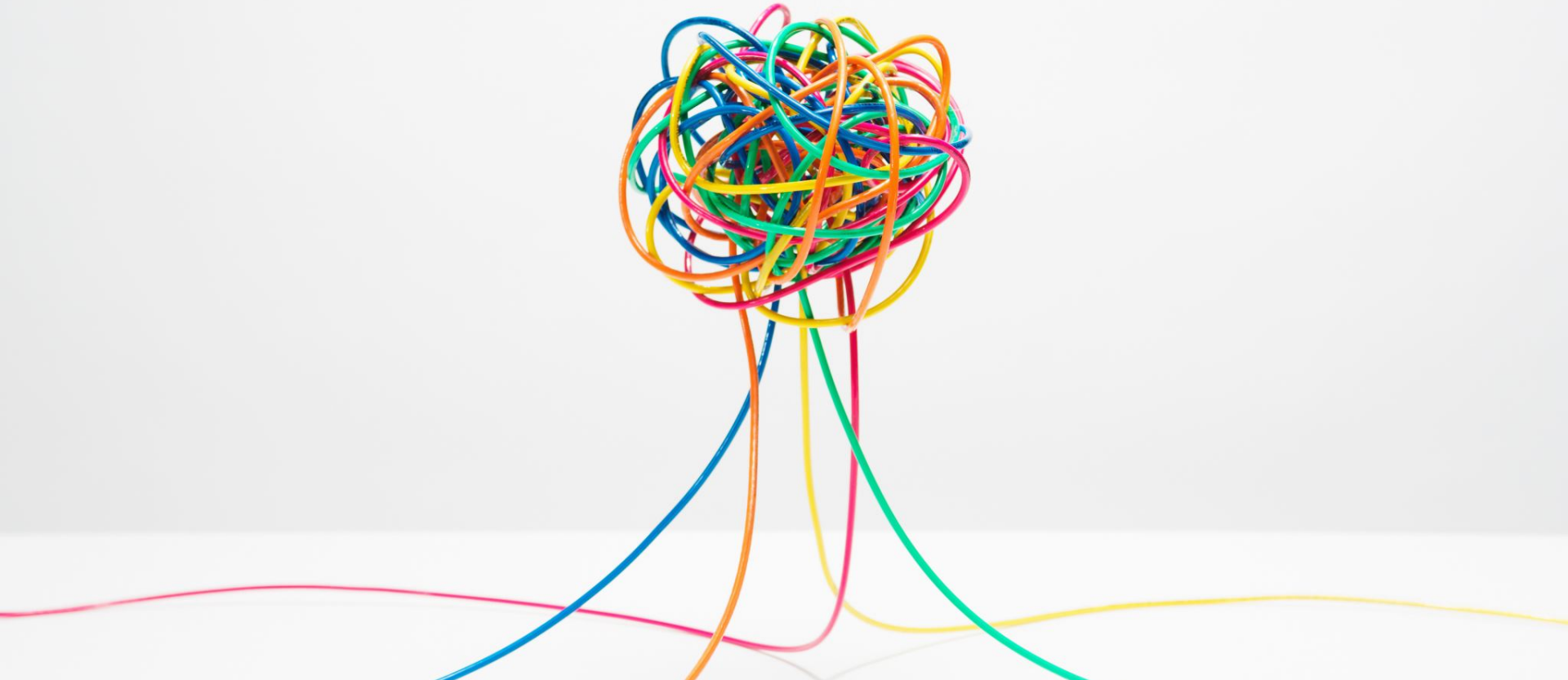


Investigating the metabolic underpinnings of early changes relevant to dementia

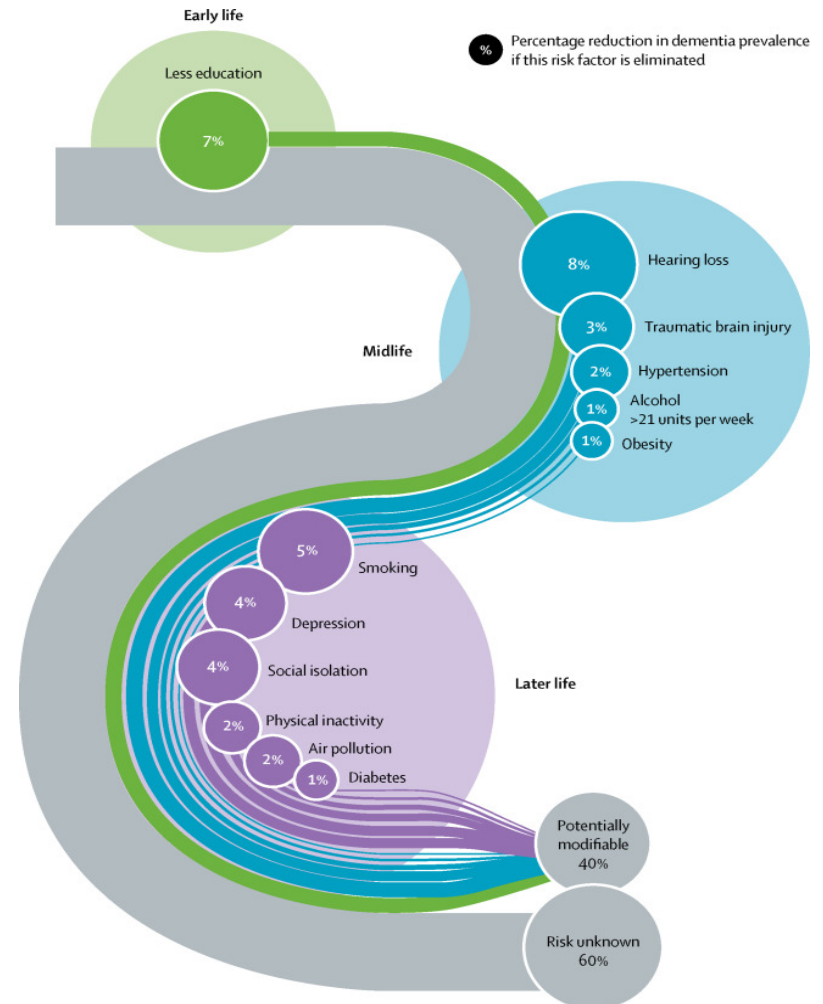
Becki Green, 3rd year PhD student, King's College London

Supervisors: Dr Petra Proitsi & Prof Marcus Richards



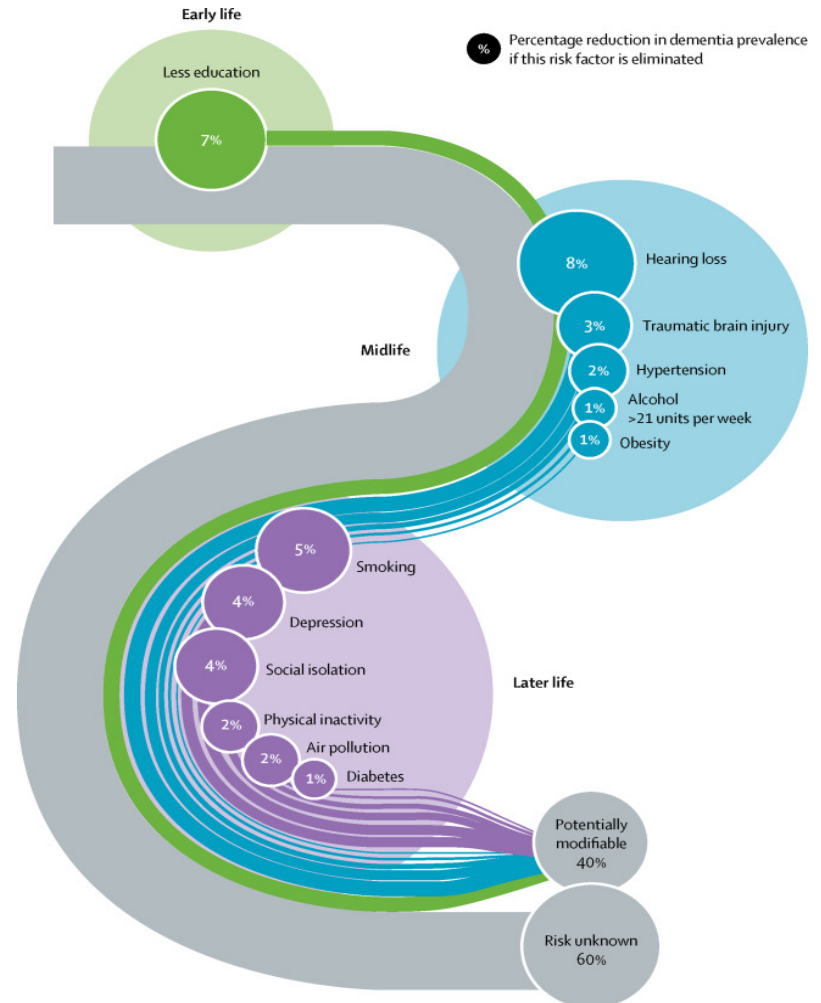
Dementia

- Impairment in cognitive functioning impeding on day to day life



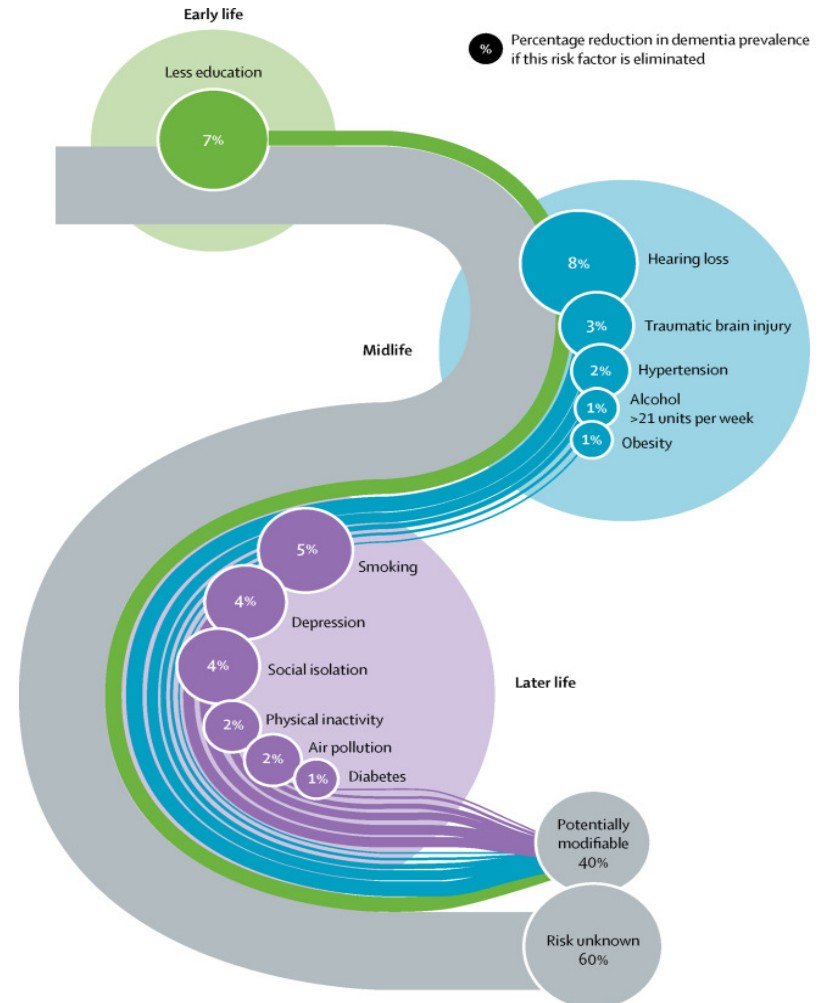
Dementia

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



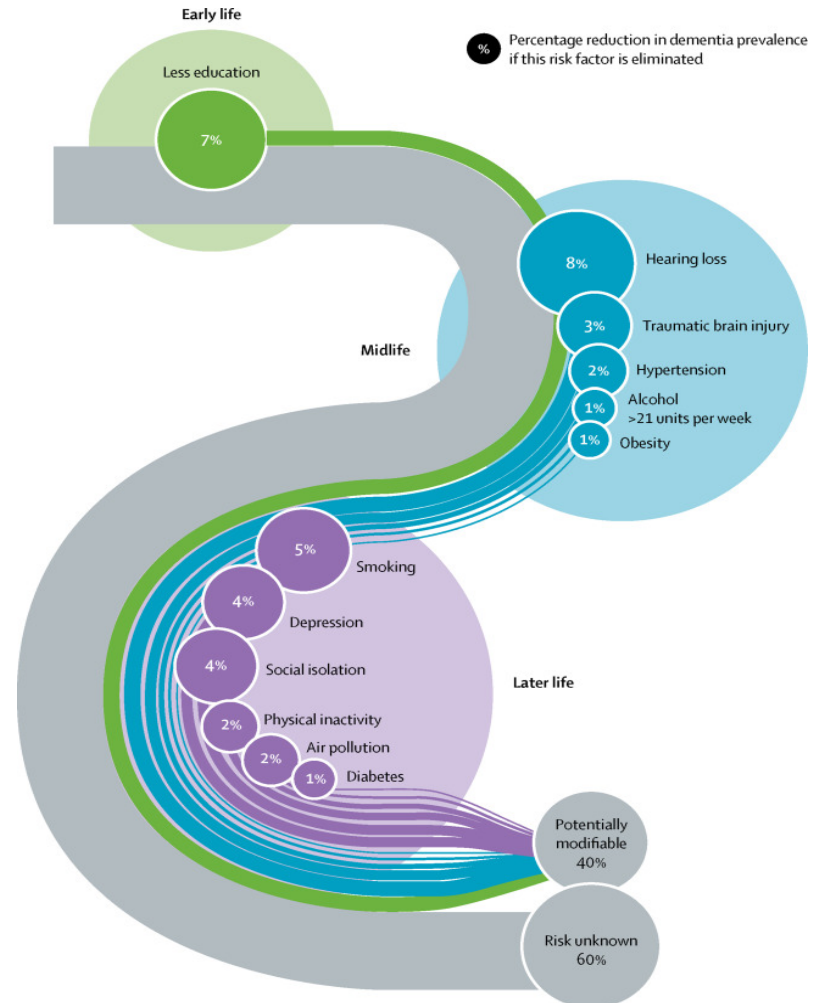
Dementia

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



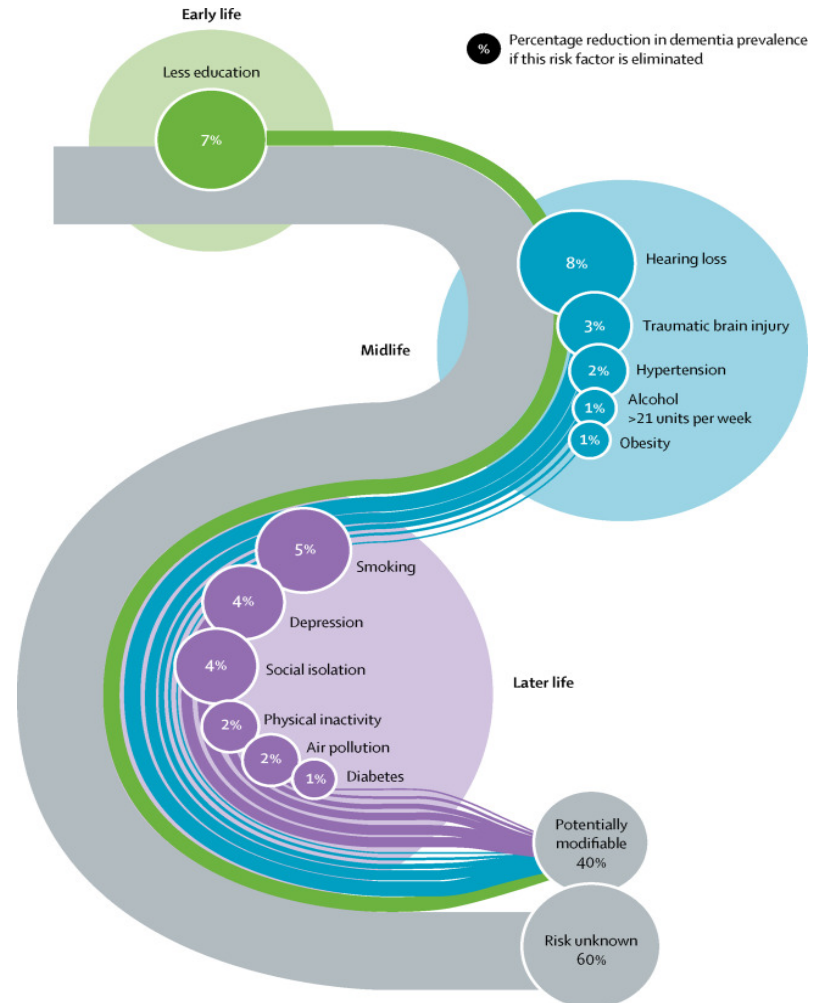
Dementia

- 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



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**



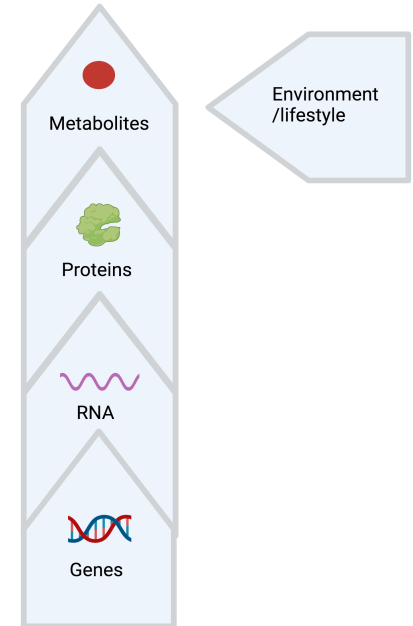
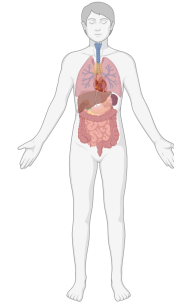
MRC 1946 British Birth Cohort Study | Insight 46

- 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



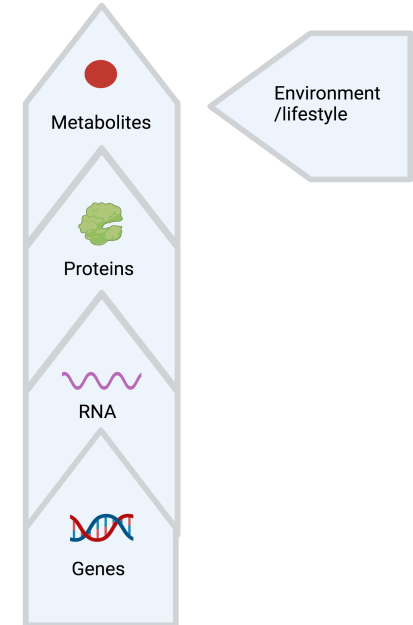
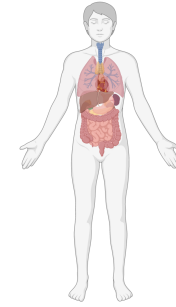
Blood metabolites

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



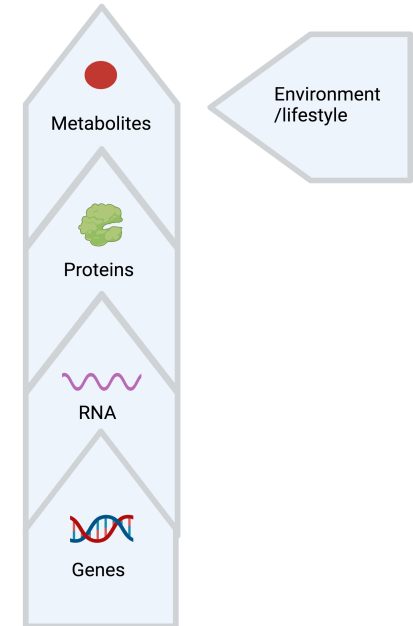
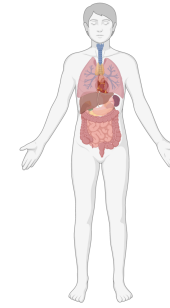
Blood metabolites

- Products of metabolism – life sustaining chemical reactions occurring in your body
- Small molecules, some can travel into the brain



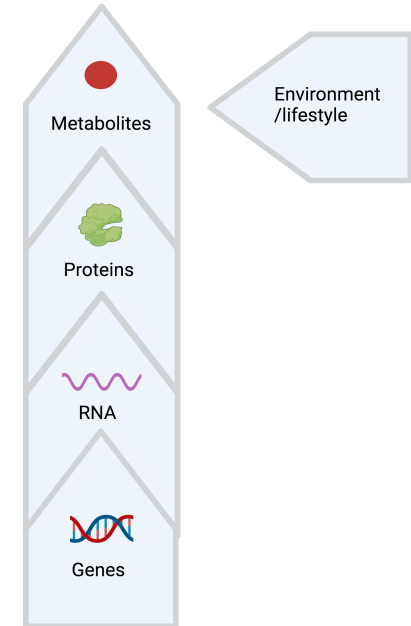
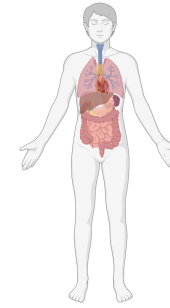
Blood metabolites

- 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



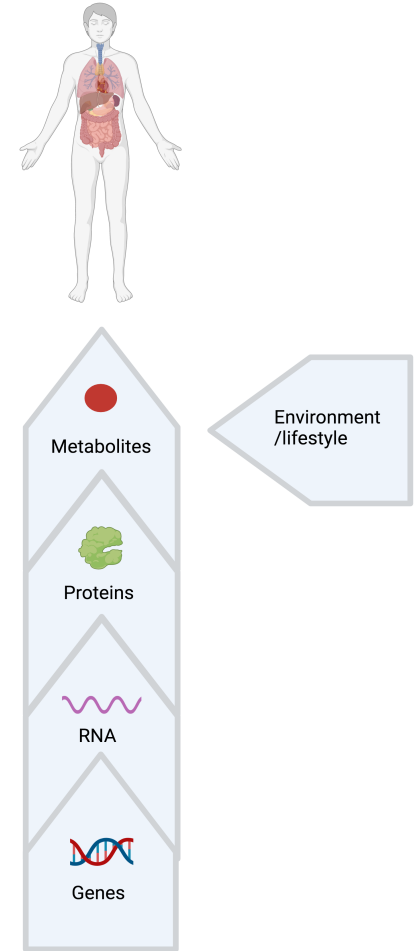
Blood metabolites

- 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

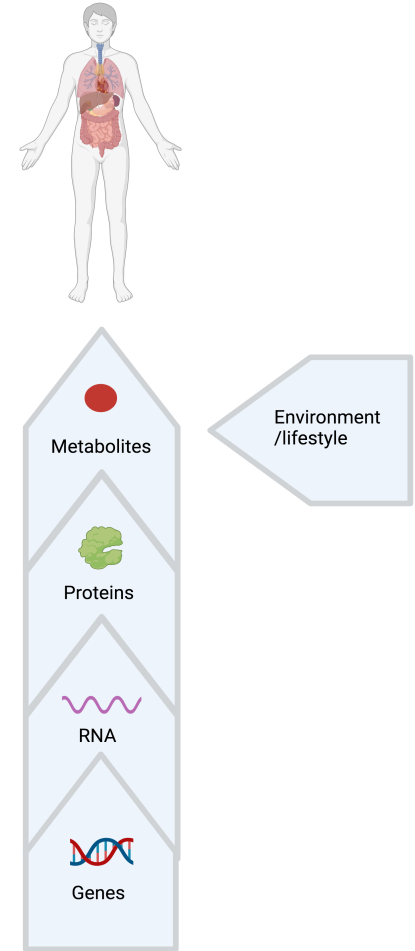
- Products of metabolism – life sustaining chemical reactions occurring in your body
- Small molecules, some can travel into the brain
- Real-time snapshot into what is going on in the body
- Accessible and potentially modifiable
- Relevant



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

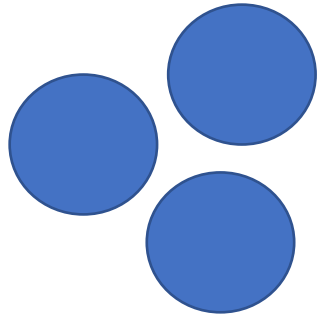
Limitations – clinical or small studies, lifestyle influences, reverse causation, replication





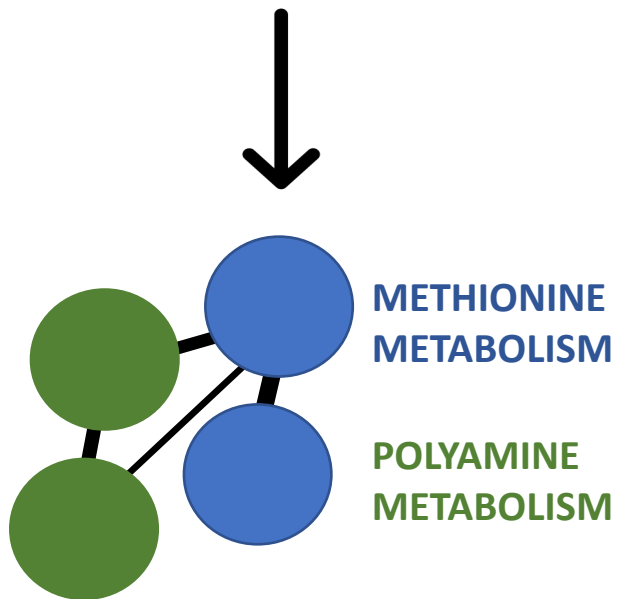
METHIONINE





**METHIONINE
METABOLISM**

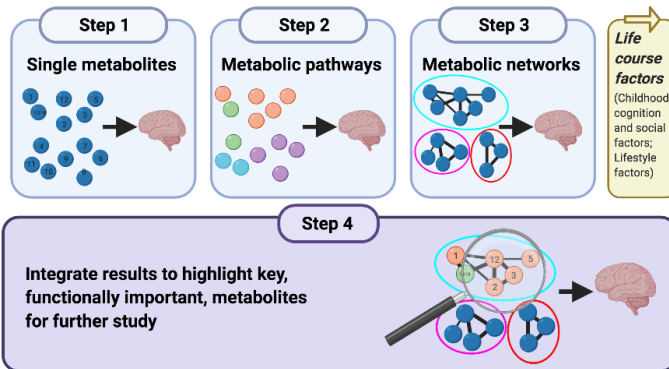




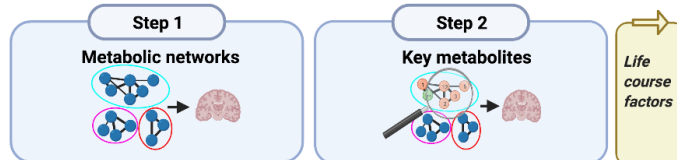
PhD aims

**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

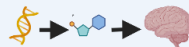


Study 2: Do key metabolites and modules also associate with brain imaging measures?



Study 3: Ascertain whether associations lie on the causal pathway

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



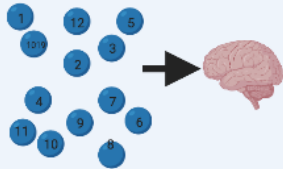
Study 4: Do related phenotypes have overlapping molecular underpinnings?

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

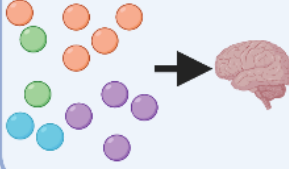
Step 1

Single metabolites



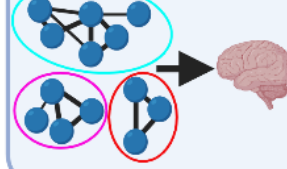
Step 2

Metabolic pathways



Step 3

Metabolic networks

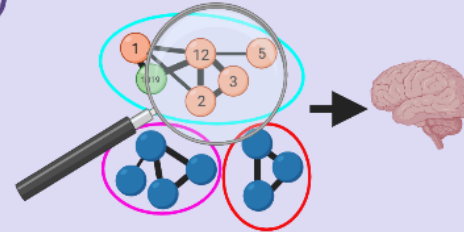


Life course factors

(Childhood cognition and social factors; Lifestyle factors)

Step 4

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

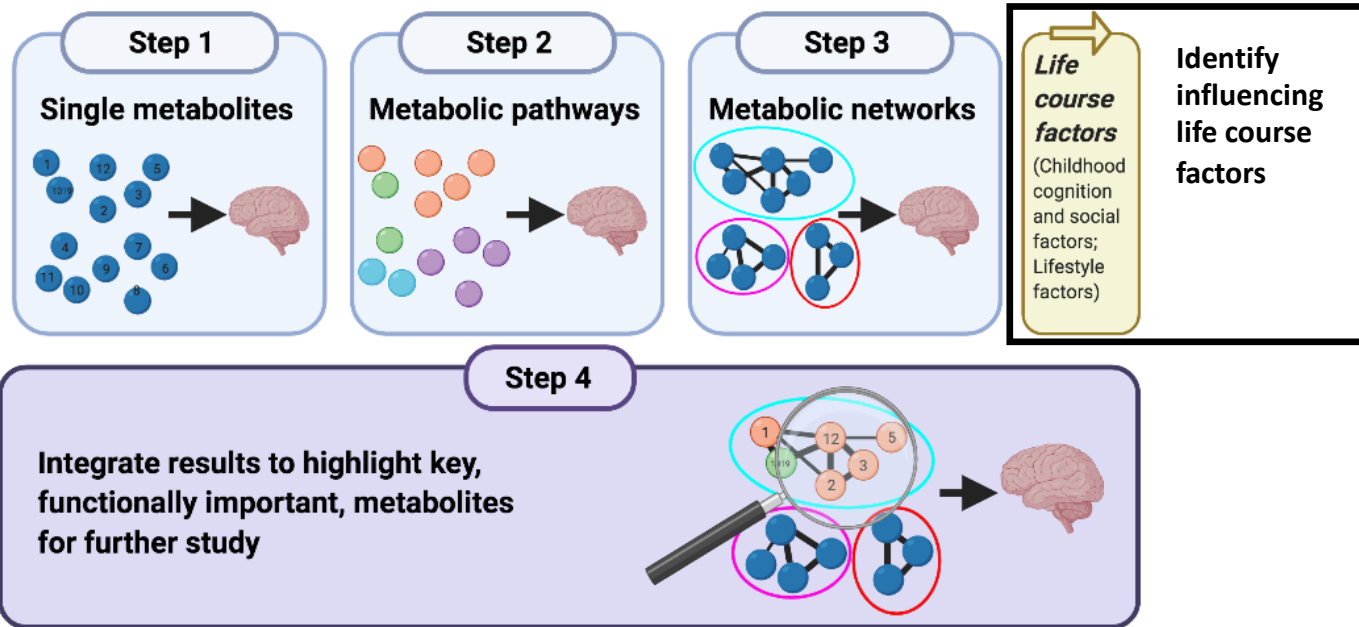


Study 2: Do key metabolites and modules also associate with brain imaging measures?

Step 1

Step 2

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



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

Step 1

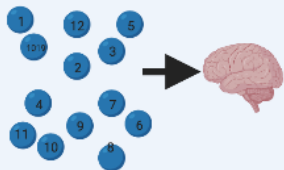
Step 2

Green et al., under review

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

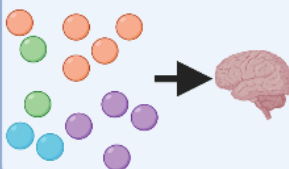
Step 1

Single metabolites



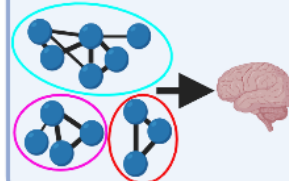
Step 2

Metabolic pathways



Step 3

Metabolic networks

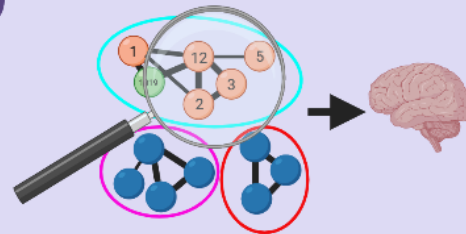


Life course factors

(Childhood cognition and social factors; Lifestyle factors)

Step 4

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



Highlight functionally important metabolites

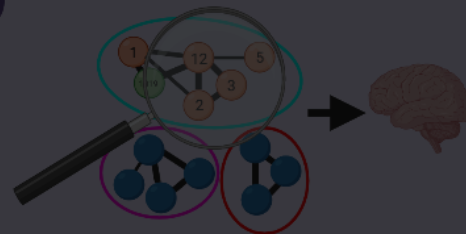
Study 2: Do key metabolites and modules also associate with brain imaging measures?

Step 1

Step 2

Step 4

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

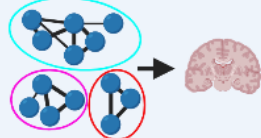


Study 2: Do key metabolites and modules also associate with brain imaging measures?

Identify modules and key metabolites associated with brain imaging measures

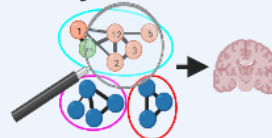
Step 1

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



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

	Cyan (n=22)	Green (n=59)	Black (n=45)	Brown (n=130)	Greenyellow (n=30)	Yellow (n=70)	Pink (n=35)	Red (n=47)	Turquoise (n=192)	Tan (n=26)	Salmon (n=25)	Blue (n=132)	Magenta (n=34)	Purple (n=33)
Memory – short-term (60–64y)	0.23 (0)	0.043 (0.08)	0.03 (0.2)	–0.075 (0.002)	0.063 (0.009)	0.099 (4e–05)	–0.0081 (0.7)	–0.039 (0.1)	–0.12 (5e–07)	–0.053 (0.03)	–0.003 (0.9)	–0.051 (0.03)	–0.034 (0.2)	–0.03 (0.2)
Memory – short-term (69y)	0.21 (3e–15)	0.033 (0.2)	–0.0065 (0.8)	–0.063 (0.02)	0.022 (0.4)	0.061 (0.02)	0.0039 (0.9)	–0.0012 (1)	–0.12 (7e–06)	–0.031 (0.2)	0.022 (0.4)	–0.021 (0.4)	–0.011 (0.7)	–0.022 (0.4)
Memory – delayed (60–64y)	0.18 (1e–13)	0.016 (0.5)	–0.00054 (1)	–0.032 (0.2)	0.043 (0.07)	0.091 (2e–04)	0.015 (0.5)	–0.025 (0.3)	–0.09 (2e–04)	–0.046 (0.05)	–0.0058 (0.8)	–0.039 (0.1)	0.0012 (1)	–0.013 (0.6)
Clinical screening measure	0.18 (1e–09)	0.081 (0.004)	–0.031 (0.3)	–0.066 (0.02)	0.031 (0.3)	0.085 (0.003)	0.0029 (0.9)	0.00038 (1)	–0.11 (2e–04)	–0.041 (0.2)	0.015 (0.6)	–0.018 (0.5)	–0.026 (0.4)	–0.045 (0.1)
Processing speed (60–64y)	0.11 (4e–06)	0.021 (0.4)	–0.008 (0.7)	–0.07 (0.004)	0.035 (0.1)	0.041 (0.09)	0.014 (0.6)	–0.037 (0.1)	–0.048 (0.05)	–0.0089 (0.7)	0.025 (0.3)	–0.034 (0.2)	–0.036 (0.1)	–0.06 (0.01)
Processing speed (69y)	0.06 (0.02)	–0.00089 (1)	–0.0054 (0.8)	–0.059 (0.02)	–0.0058 (0.8)	0.011 (0.7)	0.014 (0.6)	–0.059 (0.02)	–0.037 (0.2)	0.026 (0.3)	0.033 (0.2)	–0.032 (0.2)	–0.063 (0.02)	–0.086 (0.001)

	Cyan (n=22)	Green (n=59)	Black (n=45)	Brown (n=130)	Greenyellow (n=30)	Yellow (n=70)	Pink (n=35)	Red (n=47)	Turquoise (n=192)	Tan (n=26)	Salmon (n=25)	Blue (n=132)	Magenta (n=34)	Purple (n=33)
Memory – short-term (60–64y)	0.23 (0)	0.043 (0.08)	0.03 (0.2)	–0.075 (0.002)	0.063 (0.009)	0.099 (4e–05)	–0.0081 (0.7)	–0.039 (0.1)	–0.12 (5e–07)	–0.053 (0.03)	–0.003 (0.9)	–0.051 (0.03)	–0.034 (0.2)	–0.03 (0.2)
Memory – short-term (69y)	0.21 (3e–15)	0.033 (0.2)	–0.0065 (0.8)	–0.063 (0.02)	0.022 (0.4)	0.061 (0.02)	0.0039 (0.9)	–0.0012 (1)	–0.12 (7e–06)	–0.031 (0.2)	0.022 (0.4)	–0.021 (0.4)	–0.011 (0.7)	–0.022 (0.4)
Memory – delayed (60–64y)	0.18 (1e–13)	0.016 (0.5)	–0.00054 (1)	–0.032 (0.2)	0.043 (0.07)	0.091 (2e–04)	0.015 (0.5)	–0.025 (0.3)	–0.09 (2e–04)	–0.046 (0.05)	–0.0058 (0.8)	–0.039 (0.1)	0.0012 (1)	–0.013 (0.6)
Clinical screening measure	0.18 (1e–09)	0.081 (0.004)	–0.031 (0.3)	–0.066 (0.02)	0.031 (0.3)	0.085 (0.003)	0.0029 (0.9)	0.00038 (1)	–0.11 (2e–04)	–0.041 (0.2)	0.015 (0.6)	–0.018 (0.5)	–0.026 (0.4)	–0.045 (0.1)
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Processing speed (69y)	0.06 (0.02)	–0.00089 (1)	–0.0054 (0.8)	–0.059 (0.02)	–0.0058 (0.8)	0.011 (0.7)	0.014 (0.6)	–0.059 (0.02)	–0.037 (0.2)	0.026 (0.3)	0.033 (0.2)	–0.032 (0.2)	–0.063 (0.02)	–0.086 (0.001)

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

	Cyan (n=22)	Green (n=59)	Black (n=45)	Brown (n=130)	Greenyellow (n=30)	Yellow (n=70)	Pink (n=35)	Red (n=47)	Turquoise (n=192)	Tan (n=26)	Salmon (n=25)	Blue (n=132)	Magenta (n=34)	Purple (n=33)
Memory – short-term (60–64y)	0.23 (0)	0.043 (0.08)	0.03 (0.2)	–0.075 (0.002)	0.063 (0.009)	0.099 (4e–05)	–0.0081 (0.7)	–0.039 (0.1)	–0.12 (5e–07)	–0.053 (0.03)	–0.003 (0.9)	–0.051 (0.03)	–0.034 (0.2)	–0.03 (0.2)
Memory – short-term (69y)	0.21 (3e–15)	0.033 (0.2)	–0.0065 (0.8)	–0.063 (0.02)	0.022 (0.4)	0.061 (0.02)	0.0039 (0.9)	–0.0012 (1)	–0.12 (7e–06)	–0.031 (0.2)	0.022 (0.4)	–0.021 (0.4)	–0.011 (0.7)	–0.022 (0.4)
Memory – delayed (60–64y)	0.18 (1e–13)	0.016 (0.5)	–0.00054 (1)	–0.032 (0.2)	0.043 (0.07)	0.091 (2e–04)	0.015 (0.5)	–0.025 (0.3)	–0.09 (2e–04)	–0.046 (0.05)	–0.0058 (0.8)	–0.039 (0.1)	0.0012 (1)	–0.013 (0.6)
Clinical screening measure	0.18 (1e–09)	0.081 (0.004)	–0.031 (0.3)	–0.066 (0.02)	0.031 (0.3)	0.085 (0.003)	0.0029 (0.9)	0.00038 (1)	–0.11 (2e–04)	–0.041 (0.2)	0.015 (0.6)	–0.018 (0.5)	–0.026 (0.4)	–0.045 (0.1)
Processing speed (60–64y)	0.11 (4e–06)	0.021 (0.4)	–0.008 (0.7)	–0.07 (0.004)	0.035 (0.1)	0.041 (0.09)	0.014 (0.6)	–0.037 (0.1)	–0.048 (0.05)	–0.0089 (0.7)	0.025 (0.3)	–0.034 (0.2)	–0.036 (0.1)	–0.06 (0.01)
Processing speed (69y)	0.06 (0.02)	–0.00089 (1)	–0.0054 (0.8)	–0.059 (0.02)	–0.0058 (0.8)	0.011 (0.7)	0.014 (0.6)	–0.059 (0.02)	–0.037 (0.2)	0.026 (0.3)	0.033 (0.2)	–0.032 (0.2)	–0.063 (0.02)	–0.086 (0.001)

	Cyan (n=22)	Green (n=59)	Black (n=45)	Brown (n=130)	Greenyellow (n=30)	Yellow (n=70)	Pink (n=35)	Red (n=47)	Turquoise (n=192)	Tan (n=26)	Salmon (n=25)	Blue (n=132)	Magenta (n=34)	Purple (n=33)
Memory – short-term (60–64y)	0.068 (0.004)	–0.0074 (0.7)	–0.0045 (0.8)	0.0079 (0.7)	–0.014 (0.6)	0.0071 (0.7)	–0.025 (0.2)	–0.022 (0.3)	–0.053 (0.01)	–0.0074 (0.7)	–0.012 (0.6)	–0.026 (0.2)	–0.02 (0.3)	–0.01 (0.6)
Memory – short-term (69y)	0.066 (0.02)	–0.0078 (0.7)	–0.035 (0.1)	–0.0035 (0.9)	–0.043 (0.1)	–0.024 (0.3)	–0.015 (0.5)	0.0072 (0.8)	–0.068 (0.006)	0.0094 (0.7)	0.014 (0.6)	–0.011 (0.6)	–0.012 (0.6)	–0.013 (0.6)
Memory – delayed (60–64y)	0.042 (0.09)	–0.025 (0.3)	–0.022 (0.3)	0.029 (0.2)	–0.013 (0.6)	0.012 (0.6)	0.0017 (0.9)	–0.012 (0.6)	–0.046 (0.04)	–0.0083 (0.7)	–0.011 (0.6)	–0.016 (0.5)	0.0067 (0.8)	0.0041 (0.9)
Clinical screening measure	0.013 (0.6)	0.032 (0.2)	–0.068 (0.006)	–0.021 (0.4)	–0.038 (0.2)	–0.014 (0.6)	–0.015 (0.5)	0.0036 (0.9)	–0.065 (0.01)	0.0084 (0.7)	0.011 (0.6)	–0.013 (0.6)	–0.032 (0.2)	–0.04 (0.1)
Processing speed (60–64y)	0.0084 (0.8)	–0.0021 (0.9)	–0.031 (0.2)	–0.02 (0.4)	–0.0079 (0.8)	–0.0011 (1)	0.0029 (0.9)	–0.023 (0.3)	–0.0095 (0.7)	0.013 (0.6)	0.018 (0.4)	–0.027 (0.3)	–0.026 (0.3)	–0.053 (0.03)
Processing speed (69y)	–0.017 (0.6)	–0.013 (0.6)	–0.029 (0.3)	–0.026 (0.4)	–0.054 (0.07)	–0.02 (0.5)	0.0068 (0.8)	–0.049 (0.06)	–0.0093 (0.7)	0.037 (0.2)	0.023 (0.4)	–0.031 (0.3)	–0.059 (0.03)	–0.08 (0.002)

What about brain imaging? (study 2)

What about brain imaging? (study 2)

	Cyan (n=22)	Green (n=59)	Black (n=45)	Brown (n=130)	Greenyellow (n=30)	Yellow (n=70)	Pink (n=35)	Red (n=47)	Turquoise (n=192)	Tan (n=26)	Salmon (n=25)	Blue (n=132)	Magenta (n=34)	Purple (n=33)
Hippocampal vol -	0.013 (0.79)	-0.031 (0.47)	-0.045 (0.31)	-0.0095 (0.82)	0.052 (0.22)	0.13 (0.0026)	0.0083 (0.85)	-0.05 (0.24)	-0.021 (0.64)	-0.044 (0.27)	0.012 (0.78)	-0.075 (0.086)	-0.021 (0.63)	-0.083 (0.048)
Brain vol -	0.052 (0.043)	0.00088 (0.97)	0.028 (0.23)	-0.073 (0.0012)	0.053 (0.019)	0.058 (0.011)	-0.018 (0.43)	-0.023 (0.31)	-0.052 (0.026)	-0.052 (0.014)	-0.021 (0.36)	-0.064 (0.0061)	-0.049 (0.028)	-0.055 (0.013)

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

What about brain imaging? (study 2)

	Cyan (n=22)	Green (n=59)	Black (n=45)	Brown (n=130)	Greenyellow (n=30)	Yellow (n=70)	Pink (n=35)	Red (n=47)	Turquoise (n=192)	Tan (n=26)	Salmon (n=25)	Blue (n=132)	Magenta (n=34)	Purple (n=33)
Hippocampal vol -	0.013 (0.79)	-0.031 (0.47)	-0.045 (0.31)	-0.0095 (0.82)	0.052 (0.22)	0.13 (0.0026)	0.0083 (0.85)	-0.05 (0.24)	-0.021 (0.64)	-0.044 (0.27)	0.012 (0.78)	-0.075 (0.086)	-0.021 (0.63)	-0.083 (0.048)
Brain vol -	0.052 (0.043)	0.00088 (0.97)	0.028 (0.23)	-0.073 (0.0012)	0.053 (0.019)	0.058 (0.011)	-0.018 (0.43)	-0.023 (0.31)	-0.052 (0.026)	-0.052 (0.014)	-0.021 (0.36)	-0.064 (0.0061)	-0.049 (0.028)	-0.055 (0.013)

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)

	Cyan (n=22)	Green (n=59)	Black (n=45)	Brown (n=130)	Greenyellow (n=30)	Yellow (n=70)	Pink (n=35)	Red (n=47)	Turquoise (n=192)	Tan (n=26)	Salmon (n=25)	Blue (n=132)	Magenta (n=34)	Purple (n=33)
Hippocampal vol	0.033 (0.54)	-0.036 (0.39)	-0.029 (0.53)	-0.041 (0.37)	0.099 (0.045)	0.16 (0.00071)	-0.0066 (0.88)	-0.044 (0.3)	-0.068 (0.15)	-0.048 (0.24)	0.02 (0.64)	-0.078 (0.081)	-0.021 (0.62)	-0.07 (0.098)
Brain vol	0.046 (0.1)	0.0019 (0.93)	0.0097 (0.69)	-0.072 (0.0028)	0.031 (0.23)	0.049 (0.047)	-0.013 (0.59)	-0.018 (0.41)	-0.053 (0.034)	-0.046 (0.031)	-0.026 (0.25)	-0.062 (0.0076)	-0.041 (0.066)	-0.051 (0.022)

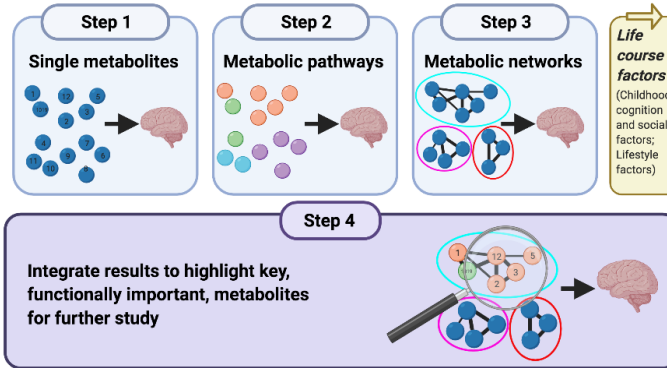
Associations persisted after adjusting for life course factors

Summary

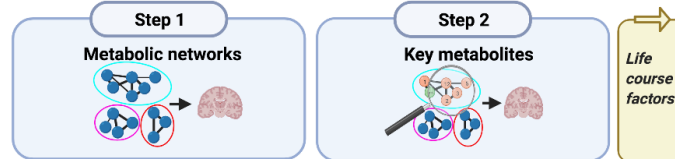
- Metabolic mechanisms highlighted:
 - Role of particular fatty acids in processing speed; role of vitamin A/C metabolites and modified nucleosides and amino acids in memory (part explained by life course factors)
 - Role of sphingolipid metabolism in hippocampal volume, phospholipids in whole brain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

Future directions

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

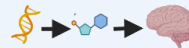


Study 2: Do key metabolites and modules also associate with brain imaging measures?



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?

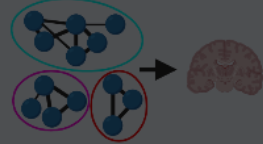
functionally important, metabolites
for further study



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

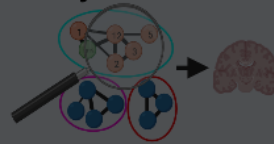
Step 1

Metabolic networks



Step 2

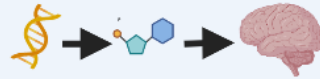
Key metabolites



*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?**

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