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Running Blue: Can an acute bout of blueberries boost post-exercise-induced benefits to brain oxygenation and cognitive function?

Submission date 08/06/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 20/06/2023	**Overall study status** Completed	
Last Edited 10/01/2025	**Condition category** Other	

Plain English summary of protocol

Background and study aims

A decline in 'our ability to think' is part of natural ageing and is partly due to deficits in blood flow delivering oxygen and nutrients to the brain. Evidence shows that being physically active improves blood flow to the brain and results in better cognition later in life. We have shown that better cognition can be seen after a single bout of exercise. As such, enhancing exercise-induced changes in brain blood flow has the potential to result in better cognition, and over the longer term optimizing the benefits of physical activity can be a way to improve resilience against cognitive decline later in life. Critically, there is evidence showing that individuals with low levels of fitness have lower increases in brain blood flow when engaging in moderate/high-intensity physical activity when compared to high-fit individuals, and this is also linked to poorer cognition. Therefore, dietary strategies, such as intake of blueberries that are rich in flavonoids, which are small molecules naturally present in cocoa, vegetables, and fruits (e.g., berries, tea, citrus fruits, and apples), prior to exercise may help to optimize the adaptive stimulus to exercise for the poor responders (low-fit), whilst still being able to maximize or accelerate benefits in good responders (high-fit). Indeed, we have previously shown that blueberries can result in immediate increases in blood flow and oxygenation in areas of the brain important for cognition, with such improvements resulting in measurable benefits in cognitive function.
The key objectives of this study are to investigate whether blueberry intake prior to low-, moderate-, and high-intensity exercise results in better brain oxygenation, which then leads to better cognitive performance. These data will establish whether blueberries might be effective in optimizing cognitive health in young healthy adults in the context of physical activity, and this work will be important to inform long-term preventive measures for ageing-associated cognitive decline, whilst providing more specific recommendations for those physically active and looking to maximize the health benefits of exercise, as well as more sedentary individuals.

Who can participate?
Healthy male and female adults aged 18-40 years old

What does the study involve?
Participants will be asked to perform a cardiorespiratory fitness test to determine their fitness

level and will only be eligible to partake in the study if they fulfil a pre-determined low-fit or high-fit criterion. Those that meet the inclusion criteria for fitness will be invited to attend two morning sessions (blueberry and placebo arm) in a fasted state at least 2 weeks apart. Baseline oxygenation, blood pressure, heart rate, and respiration will be measured continuously at rest and during an incremental cycling test. After exercise, baseline measures of executive cognitive function will be assessed whilst continuously monitoring cognitive performance-induced changes in brain oxygenation. Following these baseline measurements, participants will consume either freeze-dried highbush blueberry powder or placebo control. Measurements of brain oxygenation, blood pressure, heart rate, respiration, and cognition at rest and during exercise will be repeated 1-2 h post blueberry/control intake.

What are the possible benefits and risks of participating?
Participants will directly benefit from monetary compensation on completion of the study. Information obtained from this study may open an avenue to use blueberries to enhance the benefits of physical activity and will help identify groups of individuals most likely to benefit from blueberry intake, by quantifying and comparing the benefits across high and low-fit individuals. This work will also be highly relevant to the increasingly sedentary portion of the population, which is also at higher risk of cardiovascular disease and dementia later in life. It is estimated that ~31% of the US population is physically inactive, so finding simple and practical ways to optimize the benefits of any physical activity that takes place will likely help improve future cognitive outcomes.
The main risks of this study are an adverse reaction to the ingestion of blueberry and/or placebo supplements or a cardiovascular event during the acute bout of exercise. Routine lifestyle, health, and allergy screening safety procedures will be followed prior to participation in the study and all investigators are fully trained to supervise the exercise.

Where is the study run from?
The study is being run by the School of Sport, Exercise and Rehabilitation Sciences at The University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
August 2021 to November 2024

Who is funding the study?
US Highbush Blueberry Council (USA)

Who is the main contact?
1. Dr Catarina Rendeiro, c.rendeiro@bham.ac.uk
2. Mr Alexander Friend, a.t.friend@bham.ac.uk

Contact information

Type(s)
Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
1614398

Study information

Scientific Title
The effects of flavonoid-rich blueberry intake on cerebrovascular and cognitive responses to exercise in low and high-fit young adults

Acronym
RunBlue

Study objectives
Current study hypothesis as of 05/04/2024:
The overall aim of this study is to investigate whether intake of flavonoid-rich blueberries can improve cerebrovascular and cognitive benefits of exercise in high- and low-fit healthy individuals.

We hypothesize that the intake of blueberries prior to exercise (low, moderate and high intensity) will be an effective dietary strategy to: 1) enhance exercise-induced increases in cortical oxygenation in healthy young adults; 2) improve post-exercise cognitive performance (executive function), by enhancing local cortical oxygenation levels; and we further predict that 3) cardiorespiratory fitness will affect blueberry-induced physiological and cognitive responses to exercise, with low-fit individuals benefiting more from blueberry intake compared to high-fit individuals.

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The overall aim of this study is to investigate whether intake of flavonoid-rich blueberries can improve cerebrovascular and cognitive benefits of exercise in high- and low-fit healthy individuals.

We hypothesize that the intake of blueberries prior to exercise (low, moderate and high intensity) will be an effective dietary strategy to: 1) enhance exercise-induced increases in cortical oxygenation, cerebral blood flow/velocity and shear rate in healthy young adults; 2) improve post-exercise cognitive performance (executive function), by enhancing local cortical

oxygenation levels; and we further predict that 3) cardiorespiratory fitness will affect blueberry-induced physiological and cognitive responses to exercise, with low-fit individuals benefiting more from blueberry intake compared to high-fit individuals.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 12/06/2023, Science, Technology, Engineering and Mathematics Ethical Review Committee of the University of Birmingham) (Edgbaston, Birmingham, B15 2TT, United Kingdom; None available; aer-ethics@contacts.bham.ac.uk), ref: ERN_19-1574AP8

Study design
Acute interventional double-blinded randomized placebo-controlled crossover human study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
University/medical school/dental school

Study type(s)
Other

Participant information sheet

Health condition(s) or problem(s) studied
Low-fit and high-fit young (18-40) adults

Interventions
Current interventions as of 05/04/2024:
This study will use a randomized, placebo-controlled, double-blinded, acute human study in healthy young adults, aged 18-40 yrs, to investigate the impact of flavonoid-rich whole blueberries, in combination with exercise, in both low-fit and high-fit individuals. Those that meet the inclusion criteria for fitness will be invited to individually attend two laboratory-based face-to-face intervention trials (approx. 5 h each) at the School of Sport, Exercise and Rehabilitation Sciences at least 2 weeks apart. Participants will have completed a 12 h overnight fast, and refrain from exercising, alcohol, caffeine, and polyphenol-rich foods for 24 h prior to the visits.

Baseline cardiorespiratory, peripheral vascular, and cerebrovascular haemodynamics will be measured continuously at rest and cardiorespiratory and cerebral haemodynamics will be measured during an incremental cycling test at low, moderate, and high-intensity exercise. After exercise, baseline measures of executive cognitive function will be assessed whilst continuously monitoring cognitive performance-induced changes in cerebral haemodynamics. Measurements will be collected by a research associate (doctorate in training) trained in non-invasive monitoring of cerebrovascular physiology, specifically duplex ultrasound, cardiovascular physiology, and cardiopulmonary exercise testing.

Following these measures, participants will consume a single dose of either freeze-dried highbush blueberry powder (approximately 30g/equivalent to 1 cup of daily recommended fruit or 190 g of fresh whole blueberry, delivering approximately 960 mg of total polyphenols) or a low-flavonoid control (isocaloric and matched for carbohydrate profile, minerals and vitamins). This blueberry dose has been shown to be effective at modulating vascular function and cognitive performance in healthy subjects. The order of trials will be decided by simple randomisation using Randomizer.org.

Post-intervention measurements at rest, and of cognitive and exercise-induced cerebral haemodynamics will be repeated at 1-2 h post blueberry/control intake, coinciding with the peak of blueberry polyphenols in circulation and also informed by our previous work showing improvements in vascular function and cognitive performance 1 h post-blueberry intake.

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Intervention Type
Supplement

Primary outcome measure

Prefrontal cortical levels of oxygenated haemoglobin concentrations measured using functional Near-Infrared Spectroscopy (fNIRS) during exercise before and 1 h following consumption of blueberry or placebo supplement

Secondary outcome measures

Previous secondary outcome measures:
1. Executive function accuracy and reaction time will be measured using the following three tasks during and post-exercise, prior to and 1.5 h following, consumption of blueberry or placebo supplement:
1.1. Modified Attention Network Task (post-exercise) measures response to cognitive load
1.2. Switch Task (post-exercise) considers cognitive flexibility with participants responding to stimuli according to two different paradigms (or rule) shifts
1.3. Modified Stroop Task (during exercise) assesses selective attention and prepotent response inhibition during decision making
2. Prefrontal cortical levels of oxygenated and deoxygenated haemoglobin concentrations during cognitive performance measured using functional Near-Infrared Spectroscopy (fNIRS) before and 1.5 h following consumption of blueberry or placebo supplement
3. Common carotid artery, internal carotid artery, and vertebral artery cerebral blood flow at rest measured using duplex ultrasound before and 2 h after blueberry or placebo supplement
4. Endothelial function - Flow-mediated dilatation of the brachial artery measured using duplex ultrasound using standardised procedures before and 2.5 h post blueberry or placebo supplement

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1.2. Switch Task (post-exercise) considers cognitive flexibility with participants responding to stimuli according to two different paradigms (or rule) shifts
1.3. Modified Stroop Task (during exercise) assesses selective attention and prepotent response inhibition during decision making
2. Prefrontal cortical levels of oxygenated and deoxygenated haemoglobin concentrations during cognitive performance measured using functional Near-Infrared Spectroscopy (fNIRS) before and 1.5 h following consumption of blueberry or placebo supplement
3. Middle cerebral artery and posterior cerebral blood velocity measured using transcranial Doppler ultrasound during exercise, during the cognitive performance and at rest, before and 1h, 1.5 h, and 2h (respectively) following consumption of blueberry or placebo supplement
4. Common carotid artery, internal carotid artery, and vertebral artery cerebral blood flow at rest measured using duplex ultrasound before and 2 h after blueberry or placebo supplement
5. Endothelial function - Flow-mediated dilatation of the brachial artery measured using duplex ultrasound using standardised procedures before and 2.5 h post blueberry or placebo supplement

Overall study start date

01/08/2021

Completion date

08/11/2024

Eligibility

Key inclusion criteria
1. Healthy male or female
2. Aged 18-40 years old
3. Have a VO2max of <34 or >41 ml/kg/min in Females or <40 or >50 ml/kg/min in Males

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
40 Years

Sex
Both

Target number of participants
64

Total final enrolment
58

Key exclusion criteria
1. Consumption of more than 21 units of alcohol per week
2. A history of cardiopulmonary, cerebrovascular, musculoskeletal affecting the limbs, respiratory, metabolic, metabolic, liver, inflammatory diseases, or neurological illness. This may include but is not limited to; blood-clotting disorders, hypertension (BP > 140/90 mmHg), diabetes mellitus, anaemia, asthma (only if you take regular/daily medication or require medication before or after exercise), immune conditions, elevated cholesterol, smokers, or have recently had prolonged bed rest.
3. Known allergy to berries
4. Consumption of a weight-reducing dietary regiment
5. Taking any dietary supplements, including fatty acids and vitamins
6. Long-term medication or have been on antibiotics for the last 3 months
7. Do not have an infection at present (e.g., cold)
8. Do not have a VO2max between Female: >34 and <41 and Male: >40 and <50 ml/kg/min

Date of first enrolment
23/06/2023

Date of final enrolment
30/09/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
School of Sport, Exercise and Rehabilitation sciences
The University of Birmingham
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Sponsor information

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Sponsor type
University/education

Website
http://www.birmingham.ac.uk/index.aspx

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Research organisation

Funder Name

U.S. Highbush Blueberry Council

Alternative Name(s)
The U.S. Highbush Blueberry Council, The United States Highbush Blueberry Council, US Highbush Blueberry Council, USHBC

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United States of America

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
30/12/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Dr Catarina Rendeiro (c.rendeiro@bham.ac.uk). Pseudo-anonymised raw data of primary and secondary outcome measures will be available to the scientific community on completion of the overall study end date, for up to 10 years in accordance with the University of Birmingham policies, for specific secondary analyses of data that have not been performed as part of our original study objectives. Material containing potentially identifying information will be non-publicly available. The anonymisation and confidentiality of data and data processing are addressed in the participant's information sheet and informed consent form for the study.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant consent form version 0.2	28/02/2023	16/06/2023	No	Yes
Participant information sheet	Patient information sheet version 0.2	27/02/2023	16/06/2023	No	Yes
Protocol file	Protocol	15/06/2023	16/06/2023	No	No