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Biomarkers of Dietary Patterns and Neuropsychological Function in Adolescents

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Ο υπογράφων φοιτητής του Διατμηματικού Μεταπτυχιακού «Διεπιστημονική Διαχείριση των Χρόνιων Νοσημάτων, της Αναπηρίας και της Γήρανσης – MSc in Interdisciplinary Management of Chronic Diseases, Disability and Ageing» του Τμήματος Κοινωνικής Εργασίας του Ελληνικού Μεσογειακού Πανεπιστημίου δηλώνω υπεύθυνα ότι η παρούσα μεταπτυχιακή διπλωματική εργασία με τίτλο: «Biomarkers of Dietary Patterns and Neuropsychological Function in Adolescents» είναι στο σύνολό της προϊόν δικής μου δουλειάς και ότι όλες οι πηγές που έχουν χρησιμοποιηθεί αναφέρονται πλήρως. Επίσης δηλώνω ότι δεν αποτελεί προϊόν οποιασδήποτε εξωτερικής μη αδειοδοτημένης βοήθειας και ότι δεν έχει υποβληθεί σε οποιοδήποτε άλλο Ίδρυμα ή Οργανισμό προς αξιολόγηση, ούτε έχει δημοσιευθεί στο παρελθόν μέρος αυτής ή στο σύνολό της.

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Abstract

Adolescence is a critical period of brain maturation during which diet may influence neuropsychological development. This thesis explores the associations between adherence to the Mediterranean diet (MD) and ultra-processed food (UPF) consumption with neuropsychological outcomes in 653 adolescents (aged 11–16) from Barcelona, assessed both cross-sectionally and longitudinally over six months.

MD adherence was measured using the KIDMED index, while UPF intake was estimated with a semi-quantitative food frequency questionnaire (FFQ) and classified according to the NOVA system. Neuropsychological functioning (attention, working memory, fluid intelligence, decision-making, emotion recognition) was assessed through standardised tests, while behavioural outcomes were evaluated using the Strengths and Difficulties Questionnaire (SDQ) and teacher-reported ADHD-DSM-IV rating scales. Multivariable generalized linear models were applied, and urinary polyphenols as well as red blood cell (RBC) membrane fatty acids were used to validate UPF intake and investigate biological mechanisms.

Cross-sectionally, higher MD adherence was associated with better executive function and fewer behavioural problems, whereas higher UPF intake was associated with more behavioural issues, greater internalising symptoms, poorer decision-making, borderline ADHD symptomatology, lower alertness, and reduced emotion recognition. Longitudinally, increased UPF consumption was linked to impaired decision-making and increased internalising problems. No significant longitudinal associations were observed for MD adherence. Biomarker analyses showed no mediation via individual polyphenols or fatty acids; however, the MD fatty acid profile was cross-sectionally associated with fewer behavioural difficulties and reduced ADHD risk.

In conclusion, greater adherence to a Mediterranean dietary pattern appears to be associated with improved cognitive and behavioural profiles. Conversely, higher consumption of UPFs shows negative associations with various neuropsychological outcomes in adolescents. Nonetheless, the limited longitudinal findings suggest complex relationships that warrant further investigation, highlighting the importance of promoting healthy dietary habits during adolescence.

Περίληψη

Η εφηβεία αποτελεί κρίσιμη περίοδο ωρίμανσης του εγκεφάλου, κατά την οποία η διατροφή μπορεί να επηρεάσει τη νευροψυχολογική ανάπτυξη. Η παρούσα διατριβή εξετάζει τη συσχέτιση μεταξύ της προσκόλλησης στη Μεσογειακή διατροφή (ΜΔ) και της κατανάλωσης υπερεπεξεργασμένων τροφίμων (ΥΕΤ) με νευροψυχολογικές εκβάσεις σε 653 εφήβους (11–16 ετών) από τη Βαρκελώνη, με αξιολόγηση τόσο συγχρονικά όσο και διαχρονικά (διάστημα 6 μηνών).

Η προσκόλληση στη ΜΔ μετρήθηκε με τον δείκτη KIDMED, ενώ η πρόσληψη ΥΕΤ εκτιμήθηκε με ημι-ποσοτικό ερωτηματολόγιο συχνότητας τροφίμων και την κατάταξη NOVA. Η νευροψυχολογική λειτουργία αξιολογήθηκε με τυποποιημένες δοκιμασίες, ενώ οι συμπεριφορικές εκβάσεις με το ερωτηματολόγιο SDQ και τις κλίμακες ΔΕΠΥ βάσει DSM-IV, οι οποίες συμπληρώθηκαν από εκπαιδευτικούς. Χρησιμοποιήθηκαν πολυπαραγοντικά γραμμικά μοντέλα, ενώ πολυφαινόλες στα ούρα και λιπαρά οξέα στις μεμβράνες των ερυθροκυττάρων αξιοποιήθηκαν για την επικύρωση της πρόσληψης ΥΕΤ και τη διερεύνηση βιολογικών μηχανισμών.

Συγχρονικά, η υψηλότερη προσκόλληση στη ΜΔ συσχετίστηκε με καλύτερη εκτελεστική λειτουργία και λιγότερα προβλήματα συμπεριφοράς, ενώ η αυξημένη κατανάλωση ΥΕΤ με περισσότερα προβλήματα συμπεριφοράς, προβλήματα εσωτερίκευσης, μειωμένη ικανότητα λήψης κερδοφόρων αποφάσεων, οριακή συμπτωματολογία ΔΕΠΥ, χαμηλότερη εγρήγορση και μειωμένη αναγνώριση συναισθημάτων. Διαχρονικά, η αυξημένη κατανάλωση ΥΕΤ συσχετίστηκε με επιδείνωση της ικανότητας λήψης αποφάσεων και αύξηση των προβλημάτων εσωτερίκευσης. Οι αναλύσεις βιοδεικτών δεν ανέδειξαν διαμεσολάβηση μέσω μεμονωμένων πολυφαινολών ή λιπαρών οξέων, ενώ το προφίλ λιπαρών οξέων της ΜΔ συσχετίστηκε συγχρονικά με λιγότερα προβλήματα συμπεριφοράς και μειωμένο κίνδυνο εμφάνισης συμπτωμάτων ΔΕΠΥ.

Συμπερασματικά, η προσκόλληση στη ΜΔ φαίνεται να σχετίζεται με βελτιωμένο γνωστικό και συμπεριφορικό προφίλ. Αντίθετα, η κατανάλωση ΥΕΤ σχετίζεται αρνητικά με τις νευροψυχολογικές εκβάσεις στους εφήβους, υπογραμμίζοντας τη σημασία υγιεινών διατροφικών προτύπων κατά την εφηβεία. Ωστόσο, οι περιορισμένες διαχρονικές συσχετίσεις υποδεικνύουν ότι οι παρατηρούμενες σχέσεις χρήζουν περαιτέρω διερεύνησης.

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Abbreviations and Acronyms

ADHD: Attention-Deficit/Hyperactivity Disorder

ANT: Attention Network Test

CI: Confidence Interval

DAG: Directed Acyclic Graph

DHA: Docosahexaenoic Acid

DSM: Diagnostic and Statistical Manual of Mental Disorders

ERT: Emotion Recognition Test

FDR: False Discovery Rate

FFQ: Food Frequency Questionnaire

GLM: General Linear Model

IL-1 β : Interleukin-1 beta

ISCED: International Standard Classification of Education

KIDMED: Mediterranean Diet Quality Index for children and adolescents

MD: Mediterranean Diet

RCT: Randomised Control Trial

PFC: Prefrontal Cortex

PMA-R: Primary Mental Abilities–Revised

RMSE: Root Mean Square Error

RT: Reaction Time

SDQ: Strengths and Difficulties Questionnaire

TNF- α : Tumour Necrosis Factor alpha

UPF: Ultra-Processed Food

WSS: WALNUTs Smart-Snack Trial

WHO: World Health Organization

Keywords: KIDMED, Mediterranean diet, Ultra-processed foods, Cognition, Behaviour, Adolescents, Neuropsychology, Mental health, Attention-Deficit/Hyperactivity Disorder.

Introduction

Adolescence represents a pivotal period of human development, marked by rapid neuropsychological growth and significant structural and functional changes in the brain, particularly within the prefrontal cortex, a region essential for higher cognitive functions such as reasoning, memory, and organizational skills (Blakemore 2012; Galvan et al. 2006). Globally, approximately one in seven adolescents experiences a mental disorder, including depression, anxiety, behavioural disorders, and Attention-Deficit/Hyperactivity Disorder (ADHD), accounting for nearly 15% of the overall disease burden in this age group (Sayal et al. 2018; WHO 2021). These conditions can negatively impact adolescent development and well-being, often leading to long-term consequences into adulthood, such as increased risk of suicide and impaired psychosocial functioning (Erskine et al. 2015).

Diet emerges as a modifiable lifestyle factor with profound implications for neuropsychological outcomes during adolescence, a sensitive developmental window when the maturing brain is particularly responsive to environmental influences (Blakemore 2012). In recent years, there has been growing interest in understanding how dietary patterns may influence behavioural, mental health, and cognitive outcomes in youth. Notably, adherence to the Mediterranean diet (MD), characterized by high consumption of minimally processed plant-based foods, healthy fats, and whole grains has been associated with more favourable behavioural and cognitive profiles in adolescents. Higher adherence to the MD is linked to fewer depressive and anxiety symptoms, better emotional well-being, and improved performance in areas such as working memory, cognitive flexibility, inhibitory control, and fluid reasoning (Castro-Quezada, Román-Viñas, and Serra-Majem 2014; O'Neil et al. 2014; Peña-Jorquera et al. 2024).

Conversely, dietary patterns marked by high consumption of ultra-processed foods (UPFs) are consistently associated with adverse mental health and cognitive outcomes. Adolescents consuming greater amounts of UPFs, including sweetened beverages and energy drinks, are more likely to experience internalising symptoms (e.g., depression, anxiety), externalising problems (e.g., hyperactivity, conduct issues) and reduced cognitive performance (Dicken and Batterham 2022; Nyaradi et al. 2014; Schwartz et al. 2015; Smith et al. 2025). These detrimental effects may extend to increased risk for ADHD-related symptoms and impaired prefrontal cortex function (Al-Sabah et al. 2020; Julvez et al. 2021; Papasideris et al. 2021).

While the evidence supporting the link between diet and neuropsychological health is mounting, most existing studies are cross-sectional and often focus on isolated outcomes, lacking robust longitudinal data and objective dietary assessment methods (Camprodon-Boadas et al. 2025; O'Neil et al. 2014). However, robust evidence from adolescent populations remains limited (Camprodon-Boadas et al. 2025; O'Neil et al. 2014). Most existing studies are cross-sectional and focus on specific behavioural, mental health, or cognitive outcomes, such as attention or working memory, rather than multiple domains. Only a few studies with repeated outcome measurements have examined a broader range of behavioural and cognitive outcomes in adolescents (Nyaradi et al. 2014; O'Neil et al. 2014). Although some have examined diet and neuropsychological outcomes in adolescents (Jacka et al. 2011; Nyaradi et al. 2014), most define "healthy" patterns using data-driven food frequency questionnaire (FFQ) methods rather than validated indices (Jacka et al. 2010; Kohlboeck et al. 2012; Oddy et al. 2009; Weng et al. 2012) and often focus on specific foods or nutrients such as high-glycaemic index breakfasts or sugary drinks instead of overall dietary patterns or UPF intake (Al-Sabah et al. 2020; Ames et al. 2014; Cooper et al. 2012; van der Wurff et al. 2016). Many rely on limited or non-validated measures for behavioural or cognitive outcomes (Al-Sabah et al. 2020; Ames et al. 2014; Fulkerson et al. 2004; Weng et al. 2012). Therefore, there is a need for longitudinal studies in adolescents using validated dietary indices and comprehensive neuropsychological assessments.

In this context, biomarkers have emerged as indispensable tools for improving the precision of dietary intake assessment and elucidating the biological pathways linking nutrition to cognitive and emotional health (Gu and Scarmeas 2011; Jenab et al. 2009; Papandreou et al. 2023). Long-chain polyunsaturated fatty acids, notably those found in foods like walnuts, are particularly important for brain health, contributing to membrane fluidity, neurotransmitter function, and neuroinflammatory regulation, processes fundamental for learning, memory, and attention (Calder 2015; Chianese et al. 2018; Julvez et al. 2021). In addition, polyphenols, a diverse group of plant-derived compounds present in foods such as nuts, berries, tea, and cocoa, have demonstrated neuroprotective effects and are associated with improved cognitive and emotional health, likely through their antioxidant, anti-inflammatory, and signalling-modulating properties (Godos et al. 2018; Spencer 2008; Vauzour et al. 2010).

In Spain, adolescent dietary habits have shifted markedly over recent decades, moving away from the traditional Mediterranean pattern toward a more Westernized, processed dietary profile (Cabrera et al. 2015; Herrera-Ramos et al. 2023; Varela-Moreiras et al. 2013). This

transition underscores the urgency of investigating how these dietary changes may be influencing neuropsychological outcomes in Spanish youth, a population at increased risk due to these evolving nutritional patterns.

Therefore, this thesis aims to examine the relationship between adherence to the Mediterranean diet, ultra-processed food intake, and neuropsychological outcomes, including behavioural, mental health, and cognitive domains among adolescents. By integrating dietary biomarkers and comprehensive outcome measures, this work seeks to advance understanding of how modern dietary patterns may shape adolescent brain health and inform effective public health strategies.

Background

1. The Mediterranean Diet

Definition and Historical Background

The MD represents a traditional dietary pattern from countries bordering the Mediterranean Sea, particularly coastal Greece (sites: Crete and Korfu) and southern Italy (sites: Crevalcore, Montegiorgio, and Rome). It is characterized by abundant consumption of plant-based foods (fruits, vegetables, legumes, nuts, whole grains, and cereals), with olive oil as the principal source of dietary fat (Willett et al. 1995). The MD includes moderate consumption of fish and seafood, low to moderate intake of dairy products (primarily cheese and yogurt), limited consumption of red and processed meats, and moderate wine consumption typically accompanying meals (Trichopoulou et al. 2003). This dietary pattern was traditionally complemented by regular physical activity, primarily through manual labour, and strong social connections through shared meals (Dernini et al. 2017).

The scientific recognition of the MD as a health-promoting dietary pattern emerged from Ancel Keys' landmark Seven Countries Study initiated in the 1950s. This prospective investigation revealed strikingly lower rates of coronary heart disease and cardiovascular mortality among Mediterranean populations compared to those in Northern Europe and the United States, despite comparable or even higher total fat intake (Keys et al. 1986). This "Mediterranean paradox" was initially attributed to the favourable fatty acid profile of the diet, particularly the high monounsaturated-to-saturated fat ratio resulting from olive oil consumption (Trichopoulou et al. 2003). Subsequent research has identified additional beneficial components, including high fibre content, abundant antioxidants, polyphenols, and omega-3 fatty acids, all contributing to the diet's anti-inflammatory and cardioprotective properties (Schwingshackl et al. 2017).

In 2013, UNESCO recognized the MD as an Intangible Cultural Heritage of Humanity (UNESCO 2013), acknowledging its significance as more than a nutritional model. The compelling evidence supporting the MD's health benefits has led to its incorporation into dietary guidelines worldwide. The World Health Organization has endorsed Mediterranean dietary principles in its nutritional recommendations (WHO 2018). Similarly, the 2020–2025 Dietary Guidelines for Americans and equivalent recommendations in countries such as Australia have explicitly endorsed dietary patterns aligned with Mediterranean principles

(National Health and Council 2013; U.S. Department of Agriculture, U.S. Department of Health, and Services 2020). This global recognition reflects the MD's unique position as a dietary pattern that unites palatability, cultural significance, health promotion, and environmental sustainability.

Mediterranean Diet and Mental Health & Behavioural Outcomes

Research increasingly suggests that adherence to the MD may be protective against mental health problems and behavioural difficulties, particularly in youth. Much of the foundational evidence comes from observational studies in adults. For example, Psaltopoulou et al. 2013 observed that high MD adherence was consistently associated with a reduced risk of depression in adults and elderly populations. Later, (Lassale et al. 2018) conducted a meta-analysis in adults and further demonstrated that higher MD adherence is associated with a lower risk of developing depression.

These findings in adults are now being extended to paediatric populations. O'Neil et al. 2014 found that children and adolescents with higher MD adherence reported fewer symptoms of anxiety and depression, highlighting the relevance of diet quality for paediatric mental health.

More recently, Masini et al. 2024 reviewed the evidence in children and adolescents and emphasized the need for further research on the MD's impact on mental health. Camprodon-Boadas et al. 2025 synthesised studies in youth and found that MD adherence was associated with significantly fewer symptoms of depression, anxiety and attention-deficit/hyperactivity disorder. These authors concluded that promoting the MD could help reduce the onset and severity of psychiatric symptoms in young populations.

Although these findings are promising, most data are cross-sectional. Nevertheless, current evidence indicates that the MD is linked with more favourable mental health and behavioural outcomes in children and adolescents.

Mediterranean Diet and Cognitive Function

Emerging evidence highlights the potential benefits of the MD for cognitive function in children and adolescents, particularly within domains such as attention, working memory, and executive function. (García-Pérez-de-Sevilla and Zapata-Lamana 2025) systematically reviewed twelve cross-sectional studies and found that greater adherence to the MD was positively associated with cognitive performance, specifically in memory, attention, and executive functions among healthy youth.

In the HELENA study, Henriksson et al. 2017 assessed attention capacity in European adolescents using the d2 Test of Attention. Their findings indicated that while overall diet quality and ideal dietary patterns were associated with better attention scores, however, adherence to the MD specifically did not show a significant association with attention.

Research from Chile by Caamaño-Navarrete et al. 2025 provides further support for the cognitive benefits of healthy dietary habits. In their study of children and adolescents, those with better food habits, including patterns consistent with the MD, demonstrated better executive functions, including attention, inhibition, working memory and cognitive flexibility.

Additionally, Carrillo-López 2023 examined Spanish schoolchildren and reported that the positive relationship between attention and academic performance was most pronounced when diet quality, as measured by adherence to the MD, was optimal, independent of weight status. This finding suggests that the MD may play a moderating role in supporting cognitive processes related to learning.

Overall, current evidence suggests that higher adherence to the MD is associated with more favourable cognitive outcomes in youth, particularly in the areas of attention, working memory and executive function. Despite these findings, most available research is cross-sectional, underscoring the need for longitudinal and intervention studies to better establish causality and clarify the specific contributions of Mediterranean dietary patterns to cognitive development.

2. Ultra-Processed Foods

Definition and Classification

UPFs are defined by the NOVA classification system, which categorizes foods based on the extent and purpose of industrial processing (Carlos A Monteiro et al. 2019). UPFs (NOVA group 4) are industrial formulations that include substances rarely or never found in home kitchens, such as hydrolysed proteins, modified starches, hydrogenated oils, and a range of additives used to mimic or enhance sensory qualities (e.g., flavours, colourants, emulsifiers, sweeteners) (Carlos A Monteiro et al. 2019). Examples of UPFs include carbonated soft drinks, packaged snacks, instant noodles, reconstituted meat products, pre-prepared frozen dishes, and mass-produced packaged breads.

The NOVA classification system distinguishes UPFs from unprocessed or minimally processed foods (group 1), processed culinary ingredients (group 2), and processed foods (group 3) (Monteiro et al. 2017). This system has been endorsed by organizations such as the Food and Agriculture Organization of the United Nations and the Pan American Health Organization and is increasingly used in nutritional epidemiology research (FAO 2019; PAHO 2019). Nevertheless, some critics argue that the system may not always clearly differentiate dietary quality from the degree of processing (Astrup and Monteiro 2022).

Ultra-Processed Foods and Mental Health and Behavioural Outcomes

A growing body of evidence links UPF consumption to adverse mental health and behavioural outcomes. A systematic review and meta-analysis demonstrated an association between higher UPF consumption and increased risk of depressive and anxiety symptoms (Lane et al. 2022). Although many of these studies focus on adults, emerging research in adolescent populations reveals similar patterns.

In a cross-sectional study of adolescents from São Paulo, Brazil, higher UPF consumption was associated with increased internalizing symptoms, including anxiety and depression, even after adjusting for potential confounders (Faisal-Cury et al. 2021). Data from the ERICA study identified a lifestyle pattern marked by high UPF intake and low consumption of unprocessed foods as strongly associated with common mental disorders in Brazilian adolescents (Silva, do Carmo, and Carvalho 2021).

Additional research has examined the interplay between UPF consumption, sedentary behaviours, and psychosocial functioning. Daily UPF intake and television viewing were independently associated with higher odds of anxiety-induced sleep disturbance among

Brazilian adolescents, with the combination of these behaviours further increasing the risk (Werneck et al. 2020; Werneck, Hoare, and Silva 2021). Loneliness and eating while watching TV or studying mediated some of these associations, particularly among girls (Werneck et al. 2021).

In European settings, higher UPF consumption was associated with higher likelihood of depressive symptoms in younger Italian adults, and this association remained even after accounting for overall diet quality (Godos et al. 2023). Similarly, findings from the NutriNet-Santé cohort in France showed a positive prospective association between the proportion of UPFs in the diet and incident depressive symptoms, with risk increasing in relation to the percentage of UPF intake (Adjibade et al. 2019).

A study of Spanish adolescents found that higher UPF consumption correlated with greater psychosocial impairment, including both internalizing and externalizing problems, and that these associations were present in both boys and girls but more pronounced in males (Reales-Moreno et al. 2022).

In summary, evidence remains scarce in adolescent populations. Whilst most studies are cross-sectional and cannot establish causality, several prospective studies in both adolescent and adult populations provide additional support for a temporal relationship between UPF intake and the development of depressive symptoms (Adjibade et al. 2019; Lane et al. 2022). Nevertheless, further longitudinal and interventional research is needed to clarify causal pathways and underlying mechanisms.

Ultra-Processed Foods and Cognitive Function

Recent research has explored the relationship between UPF consumption and cognitive outcomes in adolescents. Most available studies are cross-sectional and often focus on specific UPF components such as sugar-sweetened beverages, salty or sweet snacks, and energy drinks, rather than overall UPF intake. This approach may underestimate the broader impact of UPF-rich dietary patterns.

Several cross-sectional studies report modest associations between higher consumption of these UPF components and lower cognitive performance in domains such as inhibitory control, working memory, cognitive flexibility, attention, and language skills. For example, increased intake of sugar-sweetened beverages and snacks has been linked to poorer executive function and inhibitory control, with gender differences observed in these associations in an adolescent sample in the U.S.A. (Ames et al. 2014). Other studies indicate that higher sugar-

sweetened beverage consumption is associated with greater difficulties across multiple domains of executive function in children aged 6-12 years in China (Gui et al. 2021).

However, the findings are not always consistent. A notable cross-sectional study in Brazil assessed overall UPF consumption in adolescents using multiple 24-hour dietary recalls and a validated measure of non-verbal intelligence. Despite UPF accounting for about a quarter of total energy intake, there was no significant association between UPF consumption and cognitive performance in this low-income sample (dos Santos et al. 2024).

Longitudinal evidence is limited but suggests a potential link between unhealthy dietary patterns and cognitive outcomes. In a prospective cohort study, a Western dietary pattern characterized by high intakes of ultra-processed and fast foods was associated with diminished cognitive performance three years later in Australian adolescents, after adjusting for key confounders (Nyaradi et al. 2014a).

Adolescents in Chile with dietary patterns high in UPF and sugar had the lowest cognitive and academic achievement, whilst those with lower UPF and sugar intake performed best. This may suggest that high UPF and sugar intake is associated with poorer cognitive and academic outcomes in this setting (Peña-Jorquera et al. 2024).

However, systematic review evidence remains sparse. A rapid systematic review by Noll et al. 2021 found no eligible studies that directly assessed the effects of overall UPF intake on cognition and learning in adolescents, highlighting a significant gap in the literature.

In summary, whilst some evidence suggests that higher intake of UPF components may be associated with modest deficits in specific cognitive domains amongst adolescents, findings are inconsistent and largely based on cross-sectional data focused on individual UPF items. The few studies using comprehensive measures of UPF intake do not support a robust association with cognitive performance and systematic reviews confirm a lack of high-quality evidence.

Dietary Patterns Among Spanish Adolescents

Current dietary trends in Spain

Over recent decades, Spanish adolescents have experienced a marked shift in their dietary patterns, moving away from the traditional MD toward more Westernised, processed eating habits. The ANIBES study, a large cross-sectional analysis conducted in 2013 on a nationally representative sample of the Spanish population aged 9 to 75, revealed that adolescents now consume insufficient amounts of vegetables, cereals, and fruits, while their

intakes of red meat, sausages, sweets, and ready-to-eat meals are high. Notably, non-alcoholic beverages, processed snacks, and dairy products have become dominant components of the adolescent diet, replacing more nutrient-dense traditional foods (Partearroyo et al. 2019; Varela-Moreiras et al. 2013).

Complementing these findings, the ENALIA study, which surveyed Spanish children and adolescents aged 6 months to 17 years between 2013 and 2014, demonstrated that macronutrient intake amongst young people often exceeds recommended levels for total fat and protein, particularly from animal sources, whilst carbohydrate intake is commonly below recommendations (López-Sobaler et al. 2019). These nutritional imbalances are accompanied by a significant rise in the consumption of UPFs and sugar-sweetened beverages, especially amongst younger individuals and females, as evidenced by repeated cross-sectional data from the DRECE study spanning 1991 to 2008 (Romero Ferreiro et al. 2022).

In response to these concerning trends, Spanish dietary guidelines recommend that adolescents consume at least five servings of fruits and vegetables daily, include legumes two to three times per week, prioritise whole grains and olive oil, and limit processed meats, added sugars, and sugary beverages (**Figure 1**). These guidelines are supported by frameworks such as the updated MD Pyramid (Aranceta-Bartrina et al. 2019; Bach-Faig et al. 2011) and recent policies mandating the inclusion of fresh produce and fish in school meals (BOE, 2025).

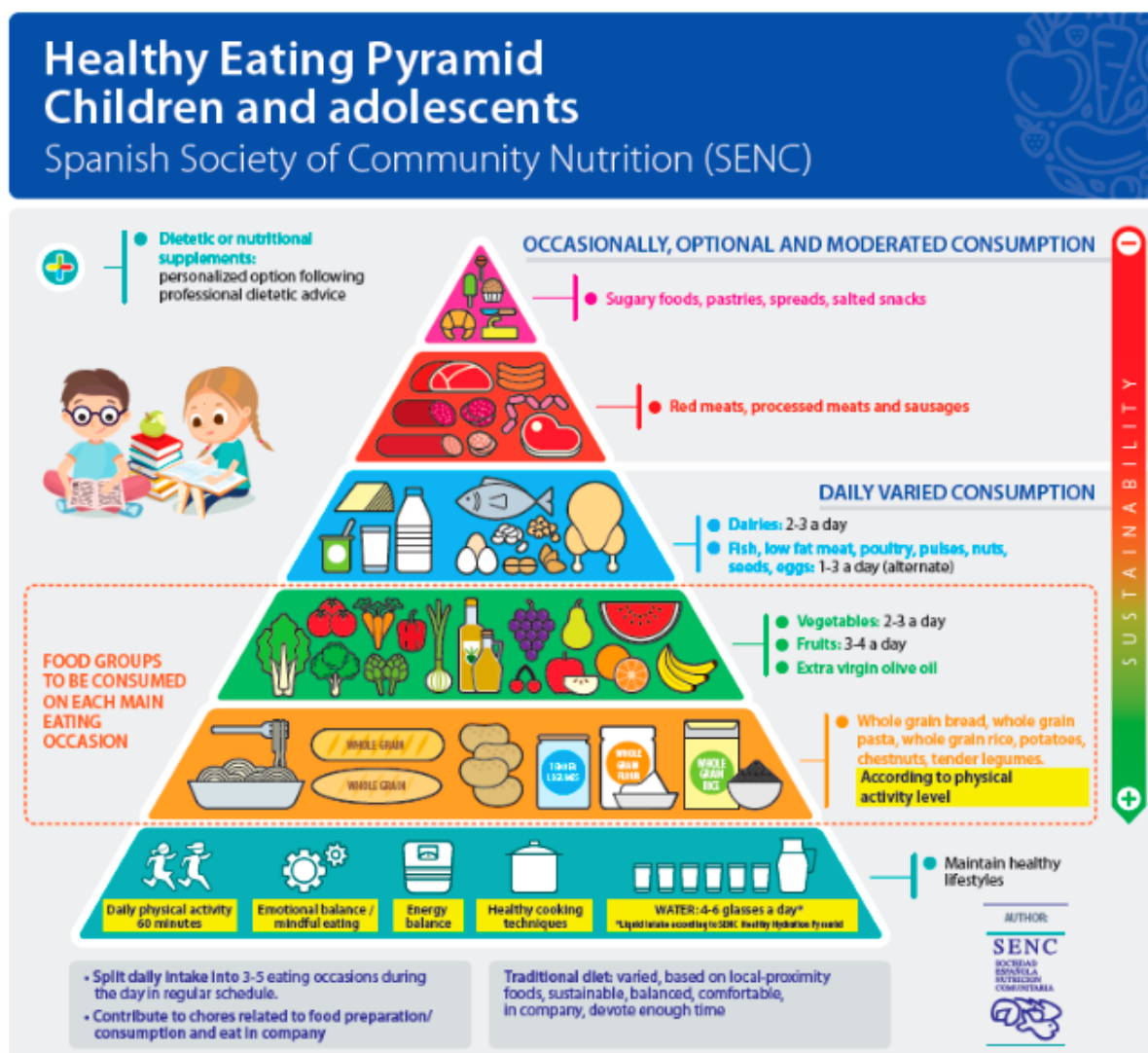


Figure 1. Healthy Eating Pyramid for children and adolescents, Spanish Society of Community (SENC)

Source: (Aranceta-Bartrina et al. 2019)

Sociodemographic and Environmental Determinants of Dietary Choices

A complex interplay of sociodemographic, environmental, and psychosocial factors shapes the dietary habits of Spanish adolescents. Multiple cross-sectional studies have shown that adolescents from families with higher parental education and income exhibit better diet quality and greater adherence to the MD, while those from lower socioeconomic backgrounds are at greater risk for poor dietary outcomes (Aranceta et al. 2003; Schröder et al. 2016). There are geographic disparities as well, with rural adolescents more likely to maintain traditional dietary patterns compared to their urban counterparts, who are exposed to more processed food environments (Grao-Cruces et al. 2013; Herrera-Ramos et al. 2023).

The family environment exerts a powerful influence on adolescent dietary behaviours. Regular family meals, as observed in cross-sectional studies of Spanish adolescents, are associated with improved food security and higher consumption of fruits and vegetables, while also being linked to reduced intake of UPFss (Barreiro-Álvarez et al. 2024). Parental modelling of healthy eating and the availability of nutritious foods at home further enhance diet quality.

Peer influences and social norms also play a significant role, as evidenced by a cross-sectional study conducted among European adolescents showing that perceived peer encouragement toward healthy eating is strongly associated with healthy eating intentions and behaviours (Stok et al. 2015).

The school environment is another critical determinant. Cross-sectional audits and observational data indicate that secondary schools in Spain often provide ready access to vending machines stocked with unhealthy snacks and beverages, which correlates with increased consumption of these products among students (Monroy-Parada et al. 2018).

Lifestyle factors such as increased screen time, sedentary behaviour, and time constraints related to academic and extracurricular commitments are associated with greater meal skipping, increased snacking, and lower adherence to healthy dietary patterns (Wärnberg et al. 2021). Moreover, the economic cost of healthy diets remains a barrier for many families; studies of Spanish youth have shown that higher monetary diet cost is positively associated with both higher diet quality and adherence to the MD, highlighting an important area for public health intervention (Schröder et al. 2016).

3. Neuropsychological Development in Adolescence

Mental Health Development in Adolescence

Adolescence is a period of heightened vulnerability for the onset of mental health conditions. Large-scale meta-analyses and epidemiological surveys show that a substantial proportion of mental health disorders first appear during youth, with approximately half of all lifetime mental disorders beginning by the mid-teens and over 60% by the mid-twenties (Solmi et al. 2022). This vulnerability is linked to ongoing neurobiological changes in the adolescent brain, including synaptic pruning, shifts in neurotransmitter systems, and the maturation of stress response pathways (Paus, Keshavan, and Giedd 2008).

Mood disorders, such as major depressive disorder, become notably more prevalent during adolescence, especially among females. The incidence of depression rises sharply after puberty, and by late adolescence, prevalence rates in girls are roughly double those in boys (Thapar et al. 2012). Anxiety disorders are also common, with epidemiological studies reporting lifetime prevalence rates of up to 30% among adolescents (Merikangas et al. 2010). Many of these conditions frequently co-occur, further increasing the burden of mental health problems during this developmental stage.

Substance use disorders often begin in adolescence, driven in part by the increased sensitivity of the developing reward system to the reinforcing properties of drugs and alcohol. Neurodevelopmental changes in motivation, impulsivity, and reward processing during adolescence may increase the risk for experimentation and the development of addictive behaviours (Chambers, Taylor, and Potenza 2003). Early exposure to substances, particularly heavy alcohol use, can disrupt normal trajectories of brain development, leading to accelerated grey matter reduction and impaired white matter growth (Squeglia et al. 2015).

Adolescence is also the typical period for the first onset of eating disorders. Pubertal changes, disturbances in body image and self-esteem, and heightened sensitivity to social evaluation all contribute to risk, especially among girls. Recent research indicates that hormonal factors, such as oestrogen activation during puberty, may play a role in increasing vulnerability to eating disorders during this time (Klump 2013).

Emerging evidence highlights the link between dietary patterns and mental health outcomes in adolescents. Healthy dietary patterns, such as the MD, are associated with a lower risk of depression and anxiety, while diets high in UPFs are linked to increased depressive symptoms and psychological distress (Khalid, Williams, and Reynolds 2016; O'Neil et al.

2014). These associations are thought to be mediated by biological mechanisms, including inflammation, oxidative stress, and changes in the gut microbiota, which can affect neurotransmitter systems and neuroplasticity (Marx et al. 2021).

The interplay between neurodevelopment, environmental influences (including nutrition), and psychosocial factors creates a complex landscape for adolescent mental health. This period is both a window of vulnerability and an opportunity for preventive interventions that can shape lifelong health and wellbeing (Patton et al. 2016).

Adolescent Brain Development

Adolescence is a pivotal phase of neurodevelopment, marked by dynamic and regionally specific changes in brain structure and function. Longitudinal MRI studies have shown that grey matter volume follows a nonlinear, inverted U-shaped trajectory: peaking in late childhood or early adolescence and then declining through adolescence and early adulthood. This decline reflects synaptic pruning, a process that eliminates excess neuronal connections and increases neural efficiency (Gogtay et al. 2004). The maturation of grey matter occurs in a specific sequence, with primary sensorimotor cortices and frontal and occipital poles maturing first, followed by a back-to-front progression across the cortex (as seen in **Figure 2**). Higher-order association areas, such as the prefrontal cortex involved in executive functions, mature last, continuing their development into the third decade of life. In contrast, brain regions associated with basic sensory processing reach maturity earlier, while the temporal cortex, especially lateral regions involved in integrative cognitive functions, matures among the latest (Gogtay et al. 2004).

White matter development also continues throughout adolescence and into adulthood. Longitudinal diffusion tensor imaging studies reveal increases in white matter volume and microstructural integrity, reflecting ongoing myelination and maturation of major tracts. While many projection and commissural tracts mature by late adolescence, association tracts continue developing into early adulthood, supporting improvements in cognitive and behavioural functions (**Figure 2**) (Lebel and Beaulieu 2011).

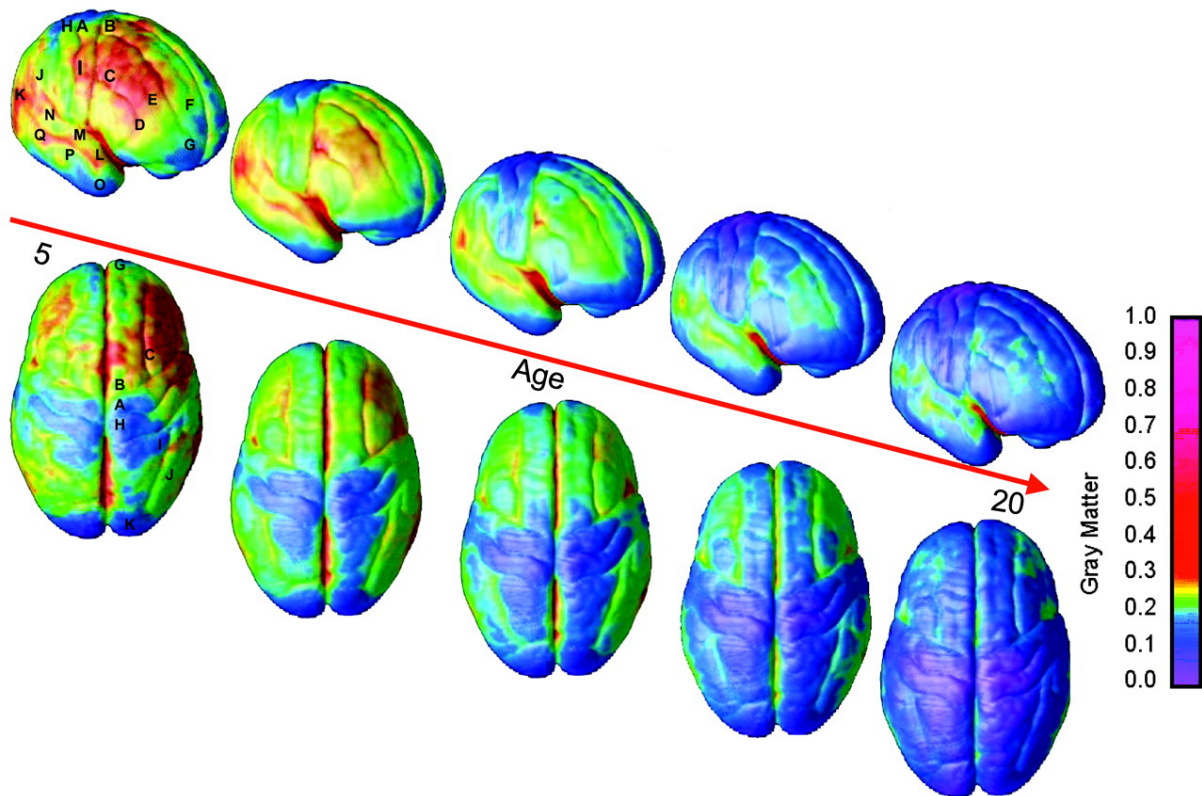


Figure 2. Gray matter (GM) maturation trajectory from ages 5 to 20 years. Right lateral and top views demonstrate the dynamic sequence of cortical development. Colours represent GM volume according to the scale bar. Maturation follows a posteroanterior progression, with primary sensorimotor regions developing earlier than association cortices and prefrontal areas.

Source: (Gogtay et al. 2004)

Functionally, these structural changes are significant. There is a developmental imbalance between limbic regions, which mature earlier and drive reward processing and emotional reactivity, and the prefrontal cortex, which matures more slowly and is responsible for cognitive control. This imbalance contributes to increased sensitivity to incentives, risk-taking, and emotional variability during adolescence (Casey, Jones, and Hare 2008).

Research suggests adolescence may be a sensitive period for brain plasticity, with heightened responsiveness to environmental influences. Studies indicate that memory, vulnerability to social stress, and susceptibility to drug use may be especially malleable during this time, offering both opportunities and risks for long-term neuropsychological outcomes. However, direct experimental evidence for adolescence as a sensitive window remains limited (Fuhrmann, Knoll, and Blakemore 2015).

This neuroplasticity confers both opportunity and vulnerability. For example, adolescent exposure to substances such as cannabis has been linked to increased risk for later psychopathology. In a large multicentre study of cocaine-dependent individuals, adolescent-onset cannabis use, especially before age 15, has been linked to an increased risk of developing cocaine-induced paranoia later in life, regardless of genetic risk (Kalayasiri et al. 2010). Thus, the adolescent brain is shaped by both biological maturation and experience and is especially sensitive to environmental factors during this period.

Cognitive Development in Adolescence

Cognitive development during adolescence is marked by significant advances in executive functions, abstract reasoning, metacognitive skills, and the capacity for self-regulation. Executive functions (EFs) encompass cognitive abilities such as inhibition (self-control and selective attention), working memory, and cognitive flexibility. These skills enable adolescents to think before acting, manage novel challenges, resist temptations, and maintain focus (Diamond 2013). While EFs begin to emerge in early childhood, they continue to strengthen throughout adolescence, with each component showing unique developmental trajectories (Best and Miller 2010).

The continued maturation of the prefrontal cortex and related neural networks supports these cognitive advances. Working memory, the capacity to hold and manipulate information, improves notably across adolescence, in line with the prolonged development of frontal brain regions (Conklin et al. 2007). This neural development underlies the increasing sophistication of executive processes and self-directed behaviour.

Adolescence is also a period of growth in abstract reasoning. The rostrolateral prefrontal cortex plays a central role in integrating abstract, self-generated thoughts. Behavioural and neuroimaging studies indicate that functions supported by this region, such as logical reasoning, relational integration, and prospective memory, continue to develop during adolescence, enabling more advanced problem-solving and planning (Dumontheil 2014).

Metacognitive abilities, including introspection and self-awareness, also improve during adolescence. Research shows that the ability to evaluate one's own decisions and confidence increases steadily through adolescence and plateaus in adulthood (Weil et al. 2013).

Cognitive development in adolescence is shaped by both neurobiological and environmental factors. Nutrition, physical activity, sleep quality, and emotional wellbeing all influence cognitive performance and brain health (Diamond 2013; Nyaradi et al. 2013). There is growing evidence that adolescence may be a sensitive period for neuroplasticity, during

which cognitive skills are especially responsive to environmental experience and training (Fuhrmann et al. 2015).

Social and emotional factors, especially peer influence, also shape adolescent cognitive development and decision-making. Adolescents are more sensitive to social rewards and peer-related stimuli, which can make risky behaviours more appealing (Albert, Chein, and Steinberg 2013; Steinberg 2008).

In summary, adolescence is a period of dynamic cognitive growth, driven by the interplay between brain maturation and environmental influences.

4. Biomarkers Of Dietary Intake

Introduction to Nutritional Biomarkers

Dietary biomarkers are objective indicators of dietary intake or nutritional status that can be measured in biological specimens such as blood, urine, adipose tissue, or hair (Dragsted et al. 2018). These biomarkers provide complementary information to traditional dietary assessment tools like FFQs and 24-hour recalls, which are prone to recall bias, social desirability bias, and errors in portion size estimation (Shim, Oh, and Kim 2014).

Dietary biomarkers are classified according to their relationship with dietary intake. Recovery biomarkers, such as doubly labelled water for energy intake and 24-hour urinary nitrogen for protein intake, reflect absolute intake over a defined time period and have a known quantitative relationship with intake (Freedman et al. 2014). Concentration biomarkers, for example serum carotenoids for fruit and vegetable intake, correlate with intake but do not provide absolute intake estimates due to individual differences in absorption, metabolism, and excretion (Jenab et al. 2009). Predictive biomarkers, like 24-hour urinary sucrose and fructose for sugar intake, share characteristics of both recovery and concentration biomarkers (Tasevska 2015). Recent evidence also suggests that urinary proline betaine can effectively calibrate FFQ data, leading to more accurate intake estimates in large cohorts. However, these biomarkers are most valuable when used within calibration frameworks alongside validated dietary assessment tools, rather than as stand-alone indicators of absolute intake (Hu et al. 2024).

Advances in metabolomics, proteomics, and related omics technologies have expanded the range of potential dietary biomarkers (Scalbert et al. 2014). Metabolomics, in particular, has enabled the identification of novel biomarkers for specific foods, food groups, and whole dietary patterns through untargeted approaches (Gibbons and Brennan 2017). These technologies have also facilitated the development of multi-metabolite biomarker panels, which may better capture complex dietary exposures than single biomarkers (Garcia-Aloy et al. 2019).

Biomarkers Associated with Mediterranean Diet Adherence

Several biomarkers have been associated with adherence to the MD, reflecting the diverse foods and nutrients characteristic of this dietary pattern. Olive oil consumption, a hallmark of the MD, can be assessed through urinary hydroxytyrosol and tyrosol, or by measuring serum oleic acid and the oleic acid to stearic acid ratio. In the PREDIMED study, urinary hydroxytyrosol increased significantly in participants assigned to a MD supplemented with extra-virgin olive oil (Estruch et al. 2013).

Biomarkers of fruit and vegetable intake, prominent components of the MD, include plasma carotenoids (such as α -carotene, β -carotene, lutein, zeaxanthin, β -cryptoxanthin, and lycopene), vitamin C, and certain flavonoids (Baldrick et al. 2011). Urinary total polyphenol excretion has also been used as a biomarker of polyphenol-rich food consumption within this dietary pattern (Medina-Remón et al. 2011).

Omega-3 fatty acids, reflecting fish consumption in the MD, can be measured in plasma, erythrocyte membranes, or adipose tissue. The omega-3 index defined as the sum of EPA and DHA in red blood cell (RBC) membranes has been widely used as a biomarker of omega-3 status in population studies (Doughty et al. 2023).

Urinary flavanones, particularly naringenin and hesperetin metabolites, serve as biomarkers for citrus fruit consumption within the Mediterranean dietary pattern (Tahiri et al. 2020). Beyond single nutrients, metabolomic approaches have identified multi-metabolite signatures of MD adherence, as shown in panels of plasma metabolites associated with MD adherence in the PREDIMED study (Guasch-Ferré et al. 2016).

Research in adolescents has found associations between MD adherence and various biomarkers, including plasma folate, β -carotene, n-3 fatty acids, vitamin D, vitamin B12, and urinary total polyphenol excretion (Iglesia et al. 2018; Vyncke et al. 2013). These biomarkers reflect the nutrient-dense nature of the Mediterranean dietary pattern and its potential benefits during this critical developmental period.

The use of biomarker panels is especially relevant for assessing adherence to dietary patterns rather than single foods. For example, a MD Biomarker Score combining plasma monounsaturated fatty acids, EPA+DHA, urinary tyrosol and hydroxytyrosol, and urinary total polyphenols has been shown to better reflect MD adherence than individual biomarkers (Sobiecki et al. 2023). The HELENA study developed a MD Biomarker Score specifically for adolescents, incorporating plasma carotenoids, serum folate, plasma vitamin C, serum vitamin B12, plasma α -linolenic acid, and urinary total polyphenol excretion, which correlated well with MD adherence as assessed by the KIDMED index (Arenaza et al. 2019).

Biomarkers of Ultra-Processed Food Intake

Unlike the MD, which has established biomarkers associated with its constituent foods, identifying specific biomarkers for UPF consumption presents challenges due to the heterogeneity of these products. However, several potential biomarkers have been proposed based on common ingredients, additives, or metabolic signatures found in UPFs.

Recent metabolomics studies have identified multi-metabolite scores in blood and urine that correlate with UPF intake, encompassing diverse metabolites such as lipids, amino acids, carbohydrates, xenobiotics, and peptides (Abar et al. 2025; Stratakis et al. 2022). These panels can objectively reflect UPF exposure and are validated across different populations and controlled feeding trials.

Building on these findings, research in adolescent and young adult populations has applied metabolomics to identify specific biomarkers of UPF intake. For example, the DONALD Cohort Study found that urine and plasma metabolite patterns reflecting xenobiotic metabolism, amino acids, and lipids were positively correlated with UPF intake, highlighting possible biological pathways linking UPFs to health outcomes (Muli et al. 2024).

Phthalates, bisphenols and other chemicals derived from food packaging are suggested as additional biomarkers of UPF intake, since these compounds can leach into foods during processing and packaging. Higher UPF consumption has been associated with higher urinary concentrations of certain phthalate and bisphenol metabolites, particularly among children and adolescents (Buckley et al. 2019; Stratakis et al. 2022).

Industrial trans fatty acids, such as elaidic acid, are produced during the partial hydrogenation of vegetable oils and are predominantly found in industrially processed foods. Plasma levels of elaidic acid have been positively associated with UPF consumption (Chajès et al. 2015).

Food additives commonly used in UPFs, including artificial sweeteners, emulsifiers, and preservatives, represent another source of potential biomarkers. Urinary excretion of artificial sweeteners such as acesulfame potassium, saccharin, and sucralose is a validated marker of UPF and ultra-processed beverage consumption (Logue et al. 2020). Emulsifiers and other additives have also been shown to affect the gut microbiome and may serve as indirect biomarkers (Naimi et al. 2021).

UPF intake has also been associated with changes in circulating protein biomarkers, including inflammatory and oxidative stress markers such as interleukin-6, TNF- α , leptin, and myeloperoxidase (He et al. 2023; Li et al. 2023; Quetglas-Llabrés et al. 2023). These findings suggest that UPF consumption may be linked not only to dietary exposure biomarkers but also to biological pathways implicated in chronic disease risk.

In adolescent and child populations, urinary metabolite profiles, including hippurate, N-methylnicotinic acid, urea, and sucrose which have been shown to discriminate UPF

consumption and diet quality (Stratakis et al. 2022). Adolescents may be particularly vulnerable to the effects of UPF-related compounds due to ongoing developmental processes.

Overall, while the field is still evolving, a combination of metabolomic signatures, chemical exposure biomarkers, and protein markers provides a promising approach to objectively assess UPF intake in both adults and younger populations.

Objectives

Purpose of the Study

This study aims to examine the associations between healthy and unhealthy dietary patterns and neuropsychological functions in adolescents.

Research Questions

1. Are healthy (MD) and unhealthy (UPF) dietary patterns associated with neuropsychological function in adolescents?
2. Do RBC membrane fatty acids (FAs) and metabolites (e.g. urinary polyphenols) link the relationship between dietary patterns and neuropsychological function?

Aims

- 1) To associate healthy and unhealthy dietary patterns with neuropsychological functioning in adolescents from the WALNUTs study.
- 2) To examine whether RBC membrane fatty acids (FAs) and urinary polyphenols mediate the relationship between these dietary patterns and neuropsychological functioning.

Research Hypotheses

H1: A healthy dietary pattern, such as the MD, is associated with improved lipid signatures and urinary polyphenol signatures and, consequently, with enhanced neuropsychological functioning, whilst an unhealthy diet, such as UPFs, is adversely associated with these signatures and neuropsychological functioning.

H0: Neither healthy nor unhealthy dietary patterns are associated with lipid signatures, urinary polyphenol signatures, or neuropsychological functioning.

Methodology

Study design and participants

This study used data from the WALNUTs Smart-Snack Trial (WSS; NCT02590848), a 6-month, multi-school randomized controlled trial evaluating the effects of daily walnut consumption on cognition and mental health in Spanish adolescents. The trial was conducted between April 2016 and June 2017 across twelve secondary schools in the Barcelona metropolitan region.

Eligible participants were adolescents aged between 11 and 16 years attending high schools in Barcelona, Spain. Exclusion criteria included those consuming regularly supplements of omega-3 poly-unsaturated fatty acids (PUFAs); already eating walnuts daily, and/or self-reported allergy to walnuts and/or gluten. Individuals were also excluded if they reported lactose intolerance or allergy to cereals, dried fruits, peanuts, soy, sesame, or sulphites, since there may be traces in walnut packages.

Of the 771 adolescents initially recruited and randomized equally to either the intervention (30 g/day raw walnut kernels) or the control groups, 653 completed the FFQ data and 649 had KIDMED index data available. For this study, we only used observational data (**Supplementary Figure 1**). Sample sizes varied by outcome variable, with both cross-sectional and longitudinal analyses conducted. Further details on trial design are available elsewhere (Julvez et al. 2021).

For this study, data were collected from schools that permitted student contact. All students in these schools were invited to participate, with actual participation being voluntary.

Primary Exposure

Dietary Assessment

Dietary intake was assessed at baseline via a semi-quantitative FFQ containing 60 items, adapted from previously validated Spanish questionnaires designed for children and pregnant women (Vioque et al. 2013, 2019). Modifications included updated portion sizes for items such as meat, fish, vegetables, rice, pasta and UPFs, as well as the inclusion of recently emerging food items (e.g., plant-based milks). Although the adapted FFQ used in this study was not independently validated, these modifications were minimal, preserving the fundamental structure and frequency categories of the original validated instruments (Vioque et al. 2013, 2019). Trained fieldworkers individually administered the FFQ during school visits, instructing participants to recall the frequency of consumption for each standardised food

portion over the past three months, ranging from "never or <1 time/month" to "≥6 times/day". All reported intakes were subsequently converted to grams per day for analyses. Adherence to the MD was considered indicative of a healthy dietary pattern, whilst UPF consumption served as a proxy for an unhealthy dietary pattern of consumption for each specified standard unit or portion size over the last 3 months.

Adherence to the Mediterranean diet

The KIDMED index is a validated tool specifically designed for children and adolescents, which evaluates the adherence to the MD (Serra-Majem et al. 2004).

The KIDMED questionnaire comprises 16 dichotomous (yes/no) items that assess both positive and negative dietary habits. Positive responses to questions reflecting healthy dietary behaviours such as daily consumption of fruits, vegetables, legumes, and the use of olive oil at home are scored with +1 point. Negative responses indicating less healthy habits such as frequent intake of fast food, sweets, and skipping breakfast are scored with -1 point (Serra-Majem et al. 2004). The total KIDMED score ranges from 0 to 12, with higher scores indicating greater adherence to the MD.

Participants completed the KIDMED questionnaire during scheduled school sessions, supervised by trained personnel to ensure consistency and accuracy in responses.

Ultra-processed food and drinks consumption

To capture a wide range of processing levels, each FFQ item was classified using the NOVA system, which distinguishes four processing categories (NOVA 1 to 4) and was applied to food items reported in the FFQs (FFQ1 at baseline and FFQ2 at follow-up) (FAO 2019; Carlos A Monteiro et al. 2019). Due to uncertainty regarding the specific products consumed by participants, a methodology similar to that used in the European Prospective Investigation into Cancer and Nutrition study was adopted (Huybrechts et al. 2022). Each food item was classified into one of four NOVA groups under three estimation scenarios to account for varying degrees of food processing.

The Lower Bound (LB) scenario assumed the lowest plausible degree of processing, considering products as traditionally or artisanally prepared and thus assigning lower NOVA classifications. The Middle Bound (MB) scenario represented the most likely classification, reflecting typical levels of processing (e.g., plain milk classified as NOVA 1). The Upper Bound (UB) scenario accounted for the possibility of higher processing (e.g., chocolate-flavored milk classified as NOVA 4 instead of plain milk as NOVA 1).

A comprehensive classification matrix was developed, categorizing all FFQ food items into NOVA groups 1-4 (minimally processed foods, processed culinary ingredients, processed foods, and UPFs, respectively) across all three scenarios. This classification was documented in an Excel file (Appendix 4, Section 1) and implemented using SPSS syntax to calculate daily intake (g/day) for each NOVA group per participant and scenario.

Reliability and agreement between the three estimation approaches were evaluated using intraclass correlation coefficient analysis, yielding a value of 0.72, which indicated acceptable agreement. Based on these results and the principle that the MB scenario best represents typical processing, the MB approach was selected for analysis. UPF intake was calculated by summing the daily consumption (g/day) of all food groups classified as ultra-processed (NOVA 4) under the MB scenario. The UPF proportion was then expressed as a percentage of total food and beverage weight consumed, following the methodology established in the PREDIMED-Plus trial (Konieczna et al. 2022). Water intake was excluded to prevent dilution of the ratio. The proportion of UPFs in the diet was categorised into tertiles, representing low (first tertile), moderate (second tertile), and high (third tertile) UPF intake levels.

For instance, if a participant consumed the following amounts in grams:

- Whole milk: 200 grams per day
- Vegetable drink: 250 grams per day
- Yoghurt: 100 grams per day

Food Item	NOVA LB
Whole milk	1
Vegetable drink	4
Yoghurt	1

The SPSS syntax was used to calculate the daily intake for each NOVA classification:

1. **NOVA 1 (Minimally Processed Foods):**
 - Total intake = 200 (whole milk) + 100 (yoghurt) = **300 grams**
2. **NOVA 4):**
 - Total intake = 250 (vegetable drink) = **250 grams**

Therefore, the participant's daily intake can be summarized as follows:

- **Daily intake of NOVA 1 foods= 300 grams**
- **Daily intake of NOVA 4 foods= 250 grams**

Biomarkers

Fatty acid Quantification

Blood samples were collected by a nurse after participants completed an overnight fast. Within four hours of collection, the samples were centrifuged at 2,500 g for 20 minutes at 20°C. A 1,500 µL aliquot of packed RBCs was extracted and stored at –80°C until fatty acid analysis was performed.

The fatty acid profile in RBCs was determined using gas chromatography, following the method described in (Sala-Vila et al. 2011). In brief, a 100 µL aliquot of RBCs was haemolysed and centrifuged to isolate the cell membranes. The membrane pellets were dissolved in 1 mL of boron trifluoride (BF₃) methanol solution and heated to facilitate the hydrolysis and methylation of glycerophospholipid fatty acids within the RBC membranes. Fatty acid methyl esters were then extracted by adding n-hexane.

Separation of the fatty acid methyl esters was achieved using gas chromatography on an Agilent HP 7890 Gas Chromatograph. The instrument was equipped with a 30 m × 0.25 µm × 0.25 mm SupraWAX-280 capillary column (Teknokroma, Barcelona, Spain), an autosampler, and a flame ionization detector. The amount of each fatty acid was calculated and expressed as a percentage of the total identified fatty acids in the sample.

Polyphenols Quantification

Urinary polyphenols were determined from first morning spot urine samples using liquid chromatography (Agilent 1290 Infinity II) coupled to high-resolution mass spectrometry (Agilent 6560 Ion Mobility QTOF LC/MS) at the Separation Techniques Unit of the Scientific and Technological Centres (CCiTUB), Universitat de Barcelona. The method was based on a previously described protocol, with minor modifications (Campins-Machado et al. 2025). Details of sample preparation, chromatographic separation, instrument parameters and quantification procedures are provided in the **Appendix 3**.

Primary Outcomes

Behavioural and Mental Health Outcomes

Behavioural outcomes were measured using the self-reported, Spanish-validated Strengths and Difficulties Questionnaire (SDQ), as well as teacher-reported ADHD symptoms using the DSM-IV checklist. These two rating scales were given to the students and teachers to be responded at home and afterwards, given back to the fieldworkers at the school visits.

Cognitive Outcomes

Cognitive outcomes were assessed at baseline and after six months using several internationally validated and standardised computer-based tests. Attention function was evaluated with the Attention Network Test (ANT), which measures three domains: alerting (difference in median reaction time [RT] for no cue vs. double cue), orienting (central cue vs. spatial cue), and executive control (incongruent vs. congruent conditions). Lower reaction times indicate better performance in these domains.

Working memory was assessed using the 4-back version of the N-back task, with detectability (d') as the outcome; higher scores reflect better performance. Fluid intelligence was measured with the Primary Mental Abilities–Revised (PMA-R), with the total score representing the number of correct responses. Decision-making ability was evaluated using the Roulettes Task, and emotion recognition was assessed with the Emotion Recognition Task (ERT). Higher scores indicate better performance for these measures.

All the computer-based tests were administered fieldwork technicians following standardised protocols to minimise measurement error and inter-observer variability. All assessments were administered by trained psychologists and fieldwork technicians at the schools after securing comfortable and quiet quarters. Computerised test outcomes were automatically recorded. Further details on each assessment are provided in **Appendix 3**.

Data Analysis

Statistical Analysis

Baseline characteristics of participants were described according to MD adherence and UPF intake groups. Continuous variables are reported as mean (standard deviation) and categorical variables as percentages. Differences between groups were assessed using Student's t-tests for BMI z-scores, Mann-Whitney U tests for other continuous variables and chi-square (χ^2) tests for categorical variables.

The proportion of UPFs was categorized into tertiles, corresponding to low (first tertile), moderate (second tertile) and high (third tertile) intake. The KIDMED score was classified into three levels: high adherence (score >8), moderate adherence (score 4–7) and low adherence (score ≤ 3). Due to the small number of participants in the low adherence category (6.8%), these individuals were combined with those in the moderate adherence category to form a single low-moderate group.

Descriptive Analysis Differences in dietary patterns between KIDMED adherence groups (low-moderate vs. high) and UPF intake categories (low, moderate, high) were assessed using one-way ANOVA or Kruskal–Wallis tests, as appropriate.

Regression Analysis For associations with neuropsychological outcomes, dietary exposures were analysed both continuously (KIDMED index score, UPF percentage of total intake) and categorically (KIDMED binary groups, UPF data-driven tertiles), with linear trend tests to evaluate dose-response relationships.

Associations with neuropsychological outcomes were examined using Generalised Linear Models (GLMs) with appropriate distributions (Gaussian, Gamma, Tweedie, or logistic), selected based on outcome distribution characteristics (e.g., skewness, kurtosis, zero-inflation). For longitudinal analyses, change scores ($\Delta = \text{follow-up} - \text{baseline}$) were analysed using Gaussian GLMs with identity links, whilst the ADHD outcome was analysed using logistic regression. All model assumptions were verified before interpretation.

Potential confounders were identified using Directed Acyclic Graphs based on literature review (**Supplementary Figures 2-3**). Final models were adjusted for age, sex (male, female), BMI z-score, maternal ethnicity (Spanish, other), substance use (no, yes), maternal educational attainment (high school studies or lower, university studies; ISCED criteria), physical activity (up to once a week, twice a week, three times a week, more than three times a week), and annual net household income (low, moderate, high). Diagnosed maternal mental

disorder (no, yes) was included as a covariate depending on the specific exposure. Longitudinal analyses additionally adjusted for randomisation group (control, intervention) and baseline outcome measurements.

Meet-in-the-Middle and Mediation Analysis Approach

To explore how dietary patterns may influence neuropsychological outcomes, two complementary analytical strategies were applied. The first approach, known as the “meet-in-the-middle” method, identifies biomarkers that are linked both to dietary intake and to brain-related outcomes such as behaviour or cognition. In this study, two types of biomarkers were considered: fatty acids in RBC membranes and urinary polyphenols. By focusing on biomarkers associated with both dietary patterns and neuropsychological outcomes, this approach helps pinpoint potential biological mediators that could explain how diet affects brain health.

The second strategy involved deriving biomarker signatures that capture the combination of fatty acids or urinary polyphenols most strongly associated with each dietary pattern. This was achieved using linear regression models with an elastic net penalty, implemented via the *glmnet* package, which enabled the selection of the most relevant biomarkers from a larger set. The relationships between these biomarker signatures and neuropsychological outcomes were then evaluated using regression models that included both the dietary pattern and the corresponding biomarker signature as predictors, while adjusting for the same set of covariates as in the primary analyses. In addition, mediation analyses were conducted using the *mediation* package to further explore potential indirect effects (Imai, Keele, and Tingley 2010).

Construction and Internal Validation of a Urinary Polyphenol Signature for UPF Consumption

A polyphenol signature for UPF intake was developed using urinary polyphenol data from 257 participants at six-month follow-up, comprising 61 polyphenols in total. Urinary polyphenols were measured only at follow-up due to financial constraints, but as UPF intake did not significantly change from baseline ($p = 0.4733$), these data were suitable for model development.

Urinary polyphenol concentrations equal to zero were recoded as missing and polyphenols with > 20% missing values were excluded from analysis, leaving 19 polyphenols for further analysis. Remaining missing values were imputed using a random forest approach implemented in the *missForest* R package (v1.5) (Stekhoven and Buehlmann 2012), with

imputation quality evaluated by normalized root mean squared error (NRMSE) and visual inspection of distributions (**Appendix 4, Section 2**). An inverse normal transformation was then applied to each imputed polyphenol to standardise distributions (**Appendix 4, Section 3**).

To account for intervention effects, UPF intake was regressed on intervention group within each training set, and the resulting residuals were used as the outcome variable in elastic net regression with all imputed and transformed polyphenol metabolites as predictors. The model was optimised through cross-validation to determine the optimal alpha ($\alpha = 0.85$) and lambda ($\lambda = 0.139470894$) parameters with the least root mean square error (RMSE = 0.021808028). Hyperparameters alpha (0.1–1; increment = 0.05) and lambda were selected by leave-one-out cross-validation (LOO-CV) within the training set to minimize root mean squared error.

Polyphenols selected as non-zero predictors in more than 80 out of 100 iterations (80%) were considered stable and retained for further analysis. Coefficients for each stable metabolite were used to construct a weighted composite polyphenol score for each participant, which was subsequently standardised to z-scores. The model underwent internal validation using 1,000 iterations of random train/test splits with a 90/10 split ratio and bootstrap resampling ($n = 10,000$). The predictive performance of the composite score was evaluated by calculating the RMSE between observed and predicted UPF intake across 1,000 random train/test splits, using only the stable metabolites as predictors.

Construction and Internal Validation of a RBC Membrane Fatty Acid Signature for UPF Consumption

A fatty acid signature for UPF intake was developed using RBC membrane fatty acid data from 322 participants at baseline. The analysis included 23 fatty acids measured in RBC membranes.

An assessment of missing data revealed complete data for all fatty acids (0% missing values), eliminating the need for imputation. All fatty acids were standardised using Z-scores to ensure comparability across variables (**Appendix 4, Section 4**).

The model was optimised through cross-validation to determine the optimal alpha ($\alpha = 0.6$) and lambda ($\lambda = 0.587399$) parameters with the least root mean square error (RMSE = 0.020095). Hyperparameters alpha (0.1–1; increment = 0.05) and lambda were selected by LOO-CV within the training set to minimize RMSE.

Fatty acids selected in over 75% of repeated random train/test splits were designated as stable predictors and included in the final signature. The model underwent internal validation

using 1,000 iterations of random train/test splits with a 90/10 split ratio and bootstrap resampling ($n = 10,000$). The model performance metrics were calculated to evaluate the predictive ability of the signature.

Construction and Internal Validation of a RBC Membrane Fatty Acid Signature for MD Adherence

A fatty acid signature for MD intake was developed using RBC membrane fatty acid data from 322 participants at baseline. The analysis included 23 fatty acids measured in RBC membranes.

An assessment of missing data revealed complete data for all fatty acids (0% missing values), eliminating the need for imputation.

The model was optimised through cross-validation to determine the optimal alpha ($\alpha = 0.25$) and lambda ($\lambda = 0.225$) parameters with the least root mean square error (RMSE = 0.0026). Hyperparameters alpha (0.1–1; increment = 0.05) and lambda were selected by LOO-CV within the training set to minimize RMSE.

Fatty acids selected in over 80% of repeated random train/test splits were designated as stable predictors and included in the final signature. The model underwent internal validation using 1,000 iterations of random train/test splits with a 90/10 split ratio and bootstrap resampling ($n = 10,000$). The model performance metrics were calculated to evaluate the predictive ability of the signature.

Missing Data

Missing covariate data were addressed using the *missForest* algorithm, a robust, non-parametric approach that handles both numeric and categorical variables. Prior to imputation, the extent of missingness was assessed, revealing up to 4.8% missing data for numeric variables and up to 26.2% for categorical variables. Post-imputation diagnostics indicated high data quality, with a normalised root mean squared error (NRMSE) of 0.144 for numeric variables and a proportion of falsely classified entries (PFC) of 0.343 for categorical variables, both within acceptable ranges. Further details are provided in **Appendix 4, Section 5**.

All analyses were conducted using R (version 4.4.2; Team R 2025).

Ethical Considerations

- **Informed Consent Form: Appendix 2**
- **Code CEIM: Appendix 2**

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Parc Salut Mar (approval number: 2015/6026/I). All participants and their legal guardians provided written informed consent at recruitment and follow-up.

- **ClinicalTrials.gov Identifier: NCT02590848**
- **Participant Information Sheet: Appendix 2**

Results

Descriptive Analysis

Participants Characteristics

A total of 649 adolescents (45.9% boys; mean age 13.8 ± 0.9 years) were included (**Table 1**). MD adherence was classified as "Poor-Average" in 60.1% and "Good" in 39.9% of participants. The mean KIDMED score was 6.8 ± 2.0 . Compared to the "Poor-Average" group, the "Good" adherence group had higher KIDMED scores (8.9 ± 1.0 vs. 5.4 ± 1.5 , $p < 0.001$), lower UPF intake ($10.6 \pm 6.2\%$ vs. $15.7 \pm 8.6\%$, $p < 0.001$), a higher proportion of male participants (52.5% vs. 41.5%, $p = 0.008$), and were slightly younger (13.7 ± 0.9 vs. 13.9 ± 0.9 years, $p = 0.009$). Substance use was higher in the "Poor-Average" group (54.6% vs. 44.0%, $p = 0.010$), whereas maternal university education was more common in the "Good" adherence group (66.4% vs. 56.7%, $p = 0.016$). No significant differences were observed for BMI z-score, maternal ethnicity, physical activity or household income.

Table 1 Baseline characteristics of the study participants, shown by categories of KIDMED index

Adolescent's Characteristics	Mediterranean Diet Adherence			p-value ¹
	Overall N =649	Low-Average N = 390	Good N = 259	
KIDMED Index Score, mean (SD)	6.8 (2.1)	5.4 (1.5)	8.9 (1.0)	< 0.001
% UPF consumption in g/d, mean (SD)	13.6 (8.1)	15.7 (8.6)	10.6 (6.2)	< 0.001
Sex, %				0.008
Male	298 (45.9%)	162 (41.5%)	136 (52.5%)	
Female	351 (54.1%)	228 (58.5%)	123 (47.5%)	
Age in years, mean (SD)	13.8 (0.9)	13.9 (0.9)	13.7 (0.9)	0.009
BMI-z score, mean (SD)	0.3 (1.1)	0.4 (1.0)	0.3 (1.1)	0.097
Substance Use ² , %				0.010
No	322 (49.6%)	177 (45.4%)	145 (56.0%)	
Yes	327 (50.4%)	213 (54.6%)	114 (44.0%)	
Physical activity, %				0.156
Up to once a week	120 (18.5%)	73 (18.7%)	47 (18.2%)	
Twice a week	165 (25.4%)	108 (27.7%)	57 (22.0%)	
Three times a week	171 (26.3%)	105 (26.9%)	66 (25.5%)	
> Three times a week	193 (29.7%)	104 (26.7%)	89 (34.4%)	
Maternal Characteristics				
Ethnicity, %				0.791
Spanish	547 (84.3%)	327 (83.9%)	220 (84.9%)	
Other	102 (15.7%)	63 (16.1%)	39 (15.1%)	
Educational Attainment, %				0.016
High school studies or lower	256 (39.4%)	169 (43.3%)	87 (33.6%)	
University studies	393 (60.6%)	221 (56.7%)	172 (66.4%)	
Annual Net Household Income, %				0.777
Low (€21k-€34k)	218 (33.6%)	134 (34.4%)	84 (32.4%)	
Moderate (€34k-€41k)	218 (33.6%)	132 (33.9%)	86 (33.2%)	
High (€41k-€84k)	213 (32.8%)	124 (31.8%)	89 (34.4%)	

Abbreviations: BMI: Body Mass Index, UPF: Ultra-Processed Food.

¹ T-Test (BMI z-score) and Mann-Whitney U tests were used for continuous variables, while Chi-Squared (χ^2) tests were conducted for categorical variables. Analyses were performed based on KIDMED categories ("Poor-Average" vs. "Good").

² Includes any of the following: cigarette, e-cigarette, alcohol, weed or other drugs.

Mean UPF consumption accounted for $13.6 \pm 8.1\%$ of total food weight (**Table 2**). KIDMED scores decreased progressively from the Low (7.6 ± 1.8) to High UPF group (5.8 ± 2.2) ($p < 0.001$). Adolescents in the High UPF group was older (14.0 ± 0.9 years vs. 13.7 ± 0.9 years, $p = 0.022$) and reported more frequent substance use (58.3%, $p = 0.010$). The proportion of mothers with university education decreased across UPF intake groups, from 66.5% in the Low to 47.7% in the High ($p < 0.001$). No significant differences were observed across UPF groups for sex distribution ($p = 0.414$), BMI z-score ($p = 0.420$), physical activity ($p = 0.854$), annual household income ($p = 0.636$), or maternal mental health disorder ($p = 0.933$). Maternal ethnicity approached significance ($p = 0.057$), with Spanish mothers representing 84.3% of the sample.

Table 2 Baseline characteristics of the study participants, shown by categories of UPF consumption

Adolescent's Characteristics	Ultra-Processed Food Consumption				p-value ¹
	Overall N = 653	Low N = 218	Moderate N = 217	High N = 218	
% UPF consumption in g/d, mean (SD)	13.6 (8.1)	6.4 (2.1)	11.9 (1.6)	22.6 (7.4)	< 0.001
KIDMED Index Score, mean (SD)	6.8 (2.1)	7.6 (1.8)	7.0 (2.1)	5.8 (2.2)	< 0.001
Sex, %					0.414
Male	300 (45.9%)	95 (43.6%)	97 (44.7%)	108 (49.5%)	
Female	353 (54.1%)	123 (56.4%)	120 (55.3%)	110 (50.5%)	
Age in years, mean (SD)	13.8 (0.9)	13.8 (0.9)	13.7 (0.9)	14.0 (0.9)	0.022
BMI-z score, mean (SD)	0.3 (1.1)	0.3 (1.0)	0.3 (1.0)	0.4 (1.2)	0.420
Substance Use ² , %					0.010
No	322 (49.6%)	112 (51.4%)	120 (55.3%)	90 (41.3%)	
Yes	327 (50.4%)	104 (47.7%)	96 (44.2%)	127 (58.3%)	
Physical activity, %					0.854
Up to once a week	120 (18.5%)	42 (19.3%)	37 (17.1%)	41 (18.8%)	
Twice a week	165 (25.4%)	58 (26.6%)	54 (24.9%)	53 (24.3%)	
Three times a week	171 (26.3%)	58 (26.6%)	53 (24.4%)	60 (27.5%)	
> Three times a week	193 (29.7%)	58 (26.6%)	72 (33.2%)	63 (28.9%)	
Maternal Characteristics					
Ethnicity, %					0.057
Spanish	547 (84.3%)	184 (84.4%)	190 (87.6%)	173 (79.4%)	
Other	102 (15.7%)	32 (14.7%)	26 (12.0%)	44 (20.2%)	
Educational Attainment, %					< 0.001
High school studies or lower	256 (39.4%)	71 (32.6%)	72 (33.2%)	113 (51.8%)	
University studies	393 (60.6%)	145 (66.5%)	144 (66.4%)	104 (47.7%)	
Annual Net Household Income, %					0.636
Low (€21k-€34k)	218 (33.6%)	73 (33.5%)	67 (30.9%)	78 (35.8%)	
Moderate (€34k-€41k)	218 (33.6%)	69 (31.7%)	73 (33.6%)	76 (34.9%)	
High (€41k-€84k)	213 (32.8%)	74 (33.9%)	76 (35.0%)	63 (28.9%)	
Maternal Mental Health Disorder, %					0.933
No	581 (89.5%)	192 (88.1%)	194 (89.4%)	195 (89.5%)	
Yes	68 (10.5%)	24 (11.0%)	22 (10.1%)	22 (11.0%)	

Abbreviations: BMI: Body Mass Index, UPF: Ultra-Processed Food.

¹ One-Way ANOVA (BMI-z score) and Kruskal-Wallis tests were used for continuous variables, while Chi-Squared (χ^2) tests were conducted for categorical variables. Analyses were performed based on UPF categories (Low, Moderate, High).

² Includes any of the following: cigarette, e-cigarette, alcohol, weed or other drugs.

Statistical Findings

Cross-sectional Associations of MD adherence and UPF consumption with Neuropsychological Outcomes

Higher KIDMED scores were consistently associated with fewer behavioural problems across all domains (**Table 3**). In fully adjusted models (model 2), each unit increase in KIDMED score was associated with a reduction in Total Behavioural Difficulties $\beta = -0.240$ (95% CI: $-0.414, -0.066$; $P = 0.007$; FDR = 0.028). Internalising Problems ($\beta = -0.106$; 95% CI: $-0.203, -0.008$; $P = 0.034$; FDR = 0.045) and Externalising Problems ($\beta = -0.134$; 95% CI: $-0.254, -0.014$; $P = 0.029$; FDR = 0.045). No significant associations were found between MD adherence and ADHD symptoms diagnosis. After FDR correction in model 2, all the SDQ scores remained significant.

Table 3 Cross-sectional associations between Mediterranean diet adherence and behavioural and mental health outcomes

Mediterranean Diet Adherence by Categories					
Outcome	Low-Average	Good β (95% CI)	Continuous β (95% CI)	P-value	FDR ⁵
Total Behavioural Difficulties Score (SDQ) ⁴					
n =	382	255	637		
Crude	Ref	-0.525 (-1.276, 0.226)	-0.289 (-0.460, -0.118)	0.001	0.004
Model 1 ¹	Ref	-0.412 (-1.168, 0.345)	-0.267 (-0.440, -0.094)	0.003	0.012
Model 2 ²	Ref	-0.291 (-1.050, 0.469)	-0.240 (-0.414, -0.066)	0.007	0.028
Internalising Problems Score (SDQ) ⁴					
n =	382	255	637		
Crude	Ref	-0.152 (-0.577, 0.273)	-0.150 (-0.246, -0.053)	0.003	0.006
Model 1 ¹	Ref	-0.017 (-0.442, 0.407)	-0.120 (-0.217, -0.023)	0.016	0.021
Model 2 ²	Ref	0.016 (-0.409, 0.441)	-0.106 (-0.203, -0.008)	0.034	0.045
Externalising Problems Score (SDQ) ⁴					
n =	382	255	637		
Crude	Ref	-0.373 (-0.893, 0.146)	-0.139 (-0.258, -0.020)	0.022	0.029
Model 1 ¹	Ref	-0.394 (-0.917, 0.128)	-0.147 (-0.267, -0.027)	0.016	0.021
Model 2 ²	Ref	-0.307 (-0.828, 0.215)	-0.134 (-0.254, -0.014)	0.029	0.045
Outcome	Low-Average	Good OR (95% CI)	Continuous OR (95% CI)	P-value	FDR ⁵
ADHD symptoms diagnosis (No/Yes)					
n =	350	233	583		
Crude	Ref	1.050 (0.606, 1.790)	0.946 (0.835, 1.070)	0.380	0.380
Model 1 ¹	Ref	0.908 (0.516, 1.570)	0.906 (0.796, 1.030)	0.132	0.132
Model 2 ²	Ref	0.938 (0.527, 1.669)	0.914 (0.802, 1.041)	0.176	0.176

Abbreviations: ADHD: Attention-Deficit/Hyperactivity Disorder, CI: Confidence Interval, FDR: False Discovery Rate, OR: Odds Ratio, SDQ: Strengths & Difficulties Questionnaire.

¹ Model 1: Adjusted for sex and age.

² Model 2: Model 1 further adjusted for BMI, ethnicity, substance use, maternal educational attainment, physical activity & annual net household income.

³ All models were estimated using generalized linear models (GLMs) with appropriate family distributions: Gaussian (identity) for internalising problems, externalising problems and behavioural problems; and logistic regression (binomial) for ADHD.

⁴ Lower scores indicate better performance.

⁵ FDR for p-value.

Regarding cognitive performance (**Table 4**), adolescents with “Good” MD adherence had significantly better Executive Attention Scores compared to the “Low–Average” group ($\beta = -6.400$; 95% CI: $-12.400, -0.418$). However, no significant associations were observed between MD adherence and other ANT domains, Fluid Intelligence, Working Memory, Emotion Recognition, nor Advantageous Risk-Taking. After FDR correction in model 2, no association remained significant.

Table 4 Cross-sectional associations between Mediterranean diet adherence and cognitive outcomes

Mediterranean Diet Adherence by Categories					
Outcome	Low-Average	Good β (95% CI)	Continuous β (95% CI)	P-value	FDR ⁶
Alerting Network Score (ANT) (ms) ⁴					
n =	370	248	618		
Crude	Ref	-0.796 (-6.870, 5.276)	-0.101 (-1.487, 1.284)	0.886	1.000
Model 1 ¹	Ref	-1.462 (-7.600, 4.676)	-0.267 (-1.670, 1.136)	0.710	0.710
Model 2 ²	Ref	-1.690 (-7.910, 4.530)	-0.269 (-1.690, 1.160)	0.712	0.720
Orienting Network Score (ANT) (ms) ⁴					
n =	370	248	618		
Crude	Ref	0.521 (-5.254, 6.296)	-0.410 (-1.727, 0.907)	0.542	0.759
Model 1 ¹	Ref	0.786 (-5.049, 6.621)	-0.348 (-1.682, 0.985)	0.609	0.710
Model 2 ²	Ref	0.112 (-5.730, 5.950)	-0.392 (-1.730, 0.946)	0.566	0.720
Executive Attention Score (ANT) (ms) ⁴					
n =	369	248	617		
Crude	Ref	-5.048 (-11.002, 0.906)	0.000 (-1.362, 1.362)	1.000	1.000
Model 1 ¹	Ref	-6.995 (-12.934, -1.056)	-0.457 (-1.821, 0.908)	0.512	0.710
Model 2 ²	Ref	-6.400 (-12.400, -0.418)	-0.252 (-1.630, 1.130)	0.720	0.720
Fluid Intelligence Score (PMA-R) ⁵					
n =	368	248	616		
Crude	Ref	0.201 (-0.686, 1.090)	0.185 (-0.017, 0.386)	0.073	0.346
Model 1 ¹	Ref	0.462 (-0.425, 1.350)	0.253 (0.051, 0.455)	0.014	0.094
Model 2 ²	Ref	0.294 (-0.578, 1.170)	0.194 (-0.005, 0.393)	0.056	0.336
Outcome	Low-Average	Good Exp(β) (95% CI)	Continuous Exp(β) (95% CI)	P-value	FDR ⁶
Working Memory Score (d'4) ⁵					
n =	364	244	608		
Crude	Ref	0.962 (0.866, 1.068)	0.986 (0.963, 1.010)	0.249	0.581
Model 1 ¹	Ref	0.966 (0.868, 1.074)	0.987 (0.964, 1.011)	0.283	0.495
Model 2 ²	Ref	0.968 (0.870, 1.076)	0.987 (0.964, 1.011)	0.281	0.502
Emotion Recognition Task Score (ERT) ⁵					
n =	369	247	616		

Crude	Ref	1.004 (0.985, 1.024)	1.002 (0.998, 1.007)	0.344	0.602
Model 1 ¹	Ref	1.015 (0.996, 1.036)	1.005 (1.001, 1.009)	0.027	0.094
Model 2 ²	Ref	1.011 (0.992, 1.031)	1.004 (0.999, 1.008)	0.096	0.336
Advantageous Risk-Taking Score (Roulettes Task) ⁵					
n =	369	247	616		
Crude	Ref	1.310 (0.879, 1.952)	1.080 (0.986, 1.183)	0.099	0.346
Model 1 ¹	Ref	1.226 (0.826, 1.818)	1.061 (0.969, 1.161)	0.202	0.471
Model 2 ²	Ref	1.166 (0.786, 1.732)	1.050 (0.959, 1.150)	0.287	0.502

Abbreviations: ANT: Attentional Network Test, CI: Confidence Interval, FDR: False Discovery Rate, PMA-R: Primary Mental Abilities–Revised.

¹ Model 1: Adjusted for sex and age.

² Model 2: Model 1 further adjusted for BMI, ethnicity, substance use, maternal educational attainment, physical activity & annual net household income.

³ All models were estimated using generalized linear models (GLMs) with appropriate family distributions: Gaussian (identity) for alerting, orienting, executive attention and fluid intelligence; Gamma (log) for risky decision-making and emotion recognition; and Tweedie (log) for working memory.

⁴ Lower scores indicate better performance.

⁵ Higher scores indicate better performance.

⁶ FDR for p-value.

As shown in Table 5, higher UPF intake was associated with increased total behavioural difficulties. In fully adjusted models, adolescents in the high tertile of UPF intake had significantly higher total behavioural difficulties scores compared to those in the low tertile ($\beta = 1.030$; 95% CI: 0.121, 1.940; $P = 0.028$), with a significant linear trend across tertiles (P -trend = 0.028). The continuous UPF measure also revealed a significant association with total behavioural difficulties ($\beta = 0.059$; 95% CI: 0.012, 0.106; $P = 0.014$). Additionally, higher UPF intake was associated with increased internalising problems ($\beta = 0.028$; 95% CI: 0.002, 0.055; $P = 0.033$). A borderline association was observed between UPF intake and ADHD symptoms diagnosis when using the continuous outcome (OR = 1.031; 95% CI: 0.999, 1.063; $P = 0.054$). However, none of these associations remained statistically significant after correction for multiple testing using the false discovery rate (all FDR > 0.05). After FDR correction in model 2, the previous associations remained of borderline significance.

Table 5 Cross-sectional associations between ultra-processed food consumption and behavioural and mental health outcomes

Ultra-Processed Food Consumption by Tertiles

Outcome	Low	Moderate β (95% CI)	High β (95% CI)	P-trend	FDR ³	Continuous β (95% CI)	P-value	FDR ⁴
Total Behavioural Difficulties Score (SDQ) ⁶								
n =	215	212	210			637		
Crude	Ref	0.087 (-0.806, 0.979)	1.136 (0.241, 2.031)	0.013	0.052	0.067 (0.022, 0.113)	0.004	0.013
Model 1 ¹	Ref	0.109 (-0.785, 1.003)	1.076 (0.179, 1.973)	0.020	0.080	0.061 (0.016, 0.107)	0.009	0.034
Model 2 ²	Ref	0.202 (-0.690, 1.090)	1.030 (0.121, 1.940)	0.028	0.112	0.059 (0.012, 0.106)	0.014	0.056
Internalising Problems Score (SDQ) ⁶								
n =	215	212	210			637		
Crude	Ref	0.053 (-0.455, 0.560)	0.456 (-0.052, 0.965)	0.080	0.106	0.025 (-0.001, 0.050)	0.061	0.061
Model 1 ¹	Ref	0.048 (-0.454, 0.550)	0.451 (-0.053, 0.955)	0.082	0.102	0.024 (-0.002, 0.050)	0.069	0.069
Model 2 ²	Ref	0.099 (-0.400, 0.597)	0.494 (-0.014, 1.000)	0.060	0.120	0.028 (0.002, 0.055)	0.033	0.063
Externalising Problems Score (SDQ) ⁶								
n =	215	212	210			637		
Crude	Ref	0.034 (-0.583, 0.652)	0.680 (0.061, 1.299)	0.033	0.066	0.043 (0.011, 0.074)	0.008	0.013
Model 1 ¹	Ref	0.061 (-0.557, 0.680)	0.625 (0.004, 1.246)	0.051	0.109	0.038 (0.006, 0.069)	0.020	0.034
Model 2 ²	Ref	0.103 (-0.511, 0.718)	0.536 (-0.090, 1.160)	0.097	0.129	0.031 (-0.002, 0.063)	0.063	0.063
Outcome	Low	Moderate OR (95% CI)	High OR (95% CI)	P-trend	FDR ³	Continuous OR (95% CI)	P-value	FDR ⁴
ADHD symptoms diagnosis (No/Yes)								
n =	192	196	195			583		
Crude	Ref	1.510 (0.763, 3.060)	1.670 (0.853, 3.350)	0.147	0.147	1.040 (1.010, 1.070)	0.010	0.013
Model 1 ¹	Ref	1.510 (0.753, 3.100)	1.580 (0.800, 3.220)	0.204	0.204	1.030 (1.000, 1.060)	0.026	0.034
Model 2 ²	Ref	1.702 (0.827, 3.502)	1.552 (0.760, 3.168)	0.247	0.247	1.031 (0.999, 1.063)	0.054	0.063

Abbreviations: ADHD: Attention-Deficit/Hyperactivity Disorder, CI: Confidence Interval, FDR: False Discovery Rate, OR: Odds Ratio, SDQ: Strengths & Difficulties Questionnaire.

¹ Model 1: Adjusted for sex and age.

² Model 2: Model 1 further adjusted for BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income & maternal mental health disorder.

³ FDR for p-trend value.

⁴ FDR for p-value.

⁵ All models were estimated using generalized linear models (GLMs) with appropriate family distributions: Gaussian (identity) for internalising problems, externalising problems and behavioural problems; and logistic regression (binomial) for ADHD.

⁶ Lower scores indicate better performance.

In terms of cognitive outcomes (**Table 6**), higher UPF intake was associated with poorer alerting network performance ($\beta = 0.421$; 95% CI: 0.039, 0.802; $P = 0.031$) and reduced accuracy in emotion recognition tasks ($\text{Exp}(\beta) = 0.998$; 95% CI: 0.997, 0.999; $P = 0.004$), with the latter also showing a significant trend across tertiles ($P\text{-trend} = 0.029$). Additionally, advantageous risk-taking was significantly lower among participants in the high vs. low UPF intake tertile ($\text{Exp}(\beta) = 0.586$; 95% CI: 0.353, 0.969; $P = 0.036$). Of these, only the association with emotion recognition remained statistically significant after FDR correction ($\text{FDR} = 0.028$), while others did not, indicating the need for cautious interpretation.

Table 6 Cross-sectional associations between ultra-processed food consumption and cognitive outcomes

Ultra-Processed Food Consumption by Tertiles								
Outcome	Low	Moderate β (95% CI)	High β (95% CI)	P-trend	FDR ³	Continuous β (95% CI)	P-value	FDR ⁴
Alerting Network Score (ANT) (ms) ⁶								
n =	210	202	206			618		
Crude	Ref	-1.571 (-8.864, 5.722)	5.351 (-1.906, 12.608)	0.152	0.355	0.402 (0.036, 0.768)	0.032	0.112
Model 1 ¹	Ref	-2.143 (-9.424, 5.137)	5.834 (-1.419, 13.088)	0.120	0.280	0.426 (0.058, 0.793)	0.024	0.084
Model 2 ²	Ref	-2.390 (-9.740, 4.960)	5.720 (-1.720, 13.200)	0.145	0.338	0.421 (0.039, 0.802)	0.031	0.108
Orienting Network Score (ANT) (ms) ⁶								
n =	210	202	206			618		
Crude	Ref	-4.710 (-11.623, 2.203)	-2.157 (-9.036, 4.722)	0.534	0.623	0.037 (-0.310, 0.385)	0.834	0.952
Model 1 ¹	Ref	-4.489 (-11.427, 2.450)	-1.264 (-8.176, 5.649)	0.709	0.827	0.089 (-0.262, 0.439)	0.620	0.723
Model 2 ²	Ref	-4.840 (-11.700, 2.050)	-0.106 (-7.080, 6.870)	0.941	0.995	0.188 (-0.170, 0.546)	0.305	0.466
Executive Attention Score (ANT) (ms) ⁶								
n =	209	202	206			617		
Crude	Ref	1.863 (-5.281, 9.006)	0.026 (-7.082, 7.134)	0.992	0.992	0.011 (-0.348, 0.369)	0.952	0.952
Model 1 ¹	Ref	1.174 (-5.930, 8.279)	0.155 (-6.922, 7.232)	0.963	0.963	0.037 (-0.321, 0.395)	0.840	0.840
Model 2 ²	Ref	0.961 (-6.160, 8.090)	-1.710 (-8.920, 5.490)	0.652	0.913	-0.072 (-0.441, 0.297)	0.702	0.819
Fluid Intelligence Score (PMA-R) ⁷								
n =	208	202	206			616		
Crude	Ref	0.624 (-0.440, 1.690)	-0.624 (-1.68, 0.435)	0.253	0.443	-0.042 (-0.096, 0.011)	0.121	0.245
Model 1 ¹	Ref	0.724 (-0.330, 1.780)	-0.524 (-1.570, 0.526)	0.339	0.505	-0.039 (-0.092, 0.014)	0.153	0.268
Model 2 ²	Ref	0.653 (-0.379, 1.690)	-0.017 (-1.060, 1.030)	0.995	0.995	-0.004 (-0.057, 0.050)	0.887	0.887
Outcome	Low	Moderate $\text{Exp}(\beta)$ (95% CI)	High $\text{Exp}(\beta)$ (95% CI)	P-trend	FDR ³	Continuous $\text{Exp}(\beta)$ (95% CI)	P-value	FDR ⁴
Working Memory Score (d'4) ⁷								
n =	208	198	202			608		
Crude	Ref	0.931 (0.822, 1.055)	0.942 (0.832, 1.067)	0.339	0.475	0.997 (0.991, 1.004)	0.384	0.538
Model 1 ¹	Ref	0.933 (0.823, 1.059)	0.945 (0.834, 1.070)	0.361	0.505	0.997 (0.991, 1.003)	0.355	0.497
Model 2 ²	Ref	0.937 (0.827, 1.063)	0.941 (0.829, 1.067)	0.331	0.579	0.997 (0.990, 1.003)	0.333	0.466
Emotion Recognition Task Score (ERT) ⁷								
n =	209	202	205			616		
Crude	Ref	1.001 (0.978, 1.025)	0.966 (0.943, 0.988)	0.003	0.021	0.998 (0.997, 0.999)	<0.001	0.002
Model 1 ¹	Ref	1.005 (0.982, 1.028)	0.968 (0.946, 0.990)	0.005	0.035	0.998 (0.997, 0.999)	<0.001	0.002
Model 2 ²	Ref	1.004 (0.981, 1.027)	0.973 (0.951, 0.997)	0.029	0.101	0.998 (0.997, 0.999)	0.004	0.028
Advantageous Risk-Taking Score (Roulettes Task) ⁷								
n =	209	202	205			616		
Crude	Ref	0.676 (0.420, 1.089)	0.593 (0.369, 0.953)	0.031	0.108	0.982 (0.959, 1.006)	0.140	0.245
Model 1 ¹	Ref	0.710 (0.445, 1.133)	0.544 (0.342, 0.868)	0.011	0.038	0.975 (0.952, 0.998)	0.036	0.084
Model 2 ²	Ref	0.688 (0.432, 1.096)	0.568 (0.353, 0.909)	0.018	0.101	0.979 (0.955, 1.003)	0.084	0.197

Abbreviations: ANT: Attentional Network Test, CI: Confidence Interval, FDR: False Discovery Rate, PMA-R: Primary Mental Abilities–Revised.

¹ Model 1: Adjusted for sex and age.

² Model 2: Model 1 further adjusted for BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income & maternal mental health disorder.

³ FDR for p-trend value.

⁴ FDR for p-value.

⁵ All models were estimated using generalized linear models (GLMs) with appropriate family distributions: Gaussian (identity) for alerting, orienting, executive attention and fluid intelligence; Gamma (log) for risky decision-making and emotion recognition; and Tweedie (log) for working memory.

⁶ Lower scores indicate better performance.

⁷ Higher scores indicate better performance.

Longitudinal Associations of MD adherence and UPF consumption with Neuropsychological Outcomes

Longitudinally, no statistically significant associations were observed between MD adherence and behavioural, mental health, or cognitive outcomes after full adjustment and correction for multiple comparisons (**Tables 7–8**).

Table 7 Longitudinal associations between Mediterranean diet adherence and behavioural and mental health outcomes

Mediterranean Diet Adherence by Categories					
Outcome	Low-Average	Good β (95% CI)	Continuous β (95% CI)	P-value	FDR ⁵
Total Behavioural Difficulties Score (SDQ) ⁴					
n =	183	144	327		
Crude	Ref	-0.215 (-1.028, 0.598)	0.110 (-0.087, 0.307)	0.276	0.368
Model 1 ¹	Ref	-0.097 (-0.846, 0.652)	0.069 (-0.113, 0.252)	0.458	0.458
Model 2 ²	Ref	-0.019 (-0.758, 0.720)	0.086 (-0.094, 0.265)	0.352	0.470
Internalising Problems Score (SDQ) ⁴					
n =	183	144	327		
Crude	Ref	-0.524 (-1.009, -0.039)	-0.027 (-0.146, 0.092)	0.655	0.655
Model 1 ¹	Ref	-0.296 (-0.720, 0.129)	-0.046 (-0.149, 0.057)	0.381	0.458
Model 2 ²	Ref	-0.272 (-0.695, 0.150)	-0.036 (-0.139, 0.066)	0.487	0.487
Externalising Problems Score (SDQ) ⁴					
n =	183	144	327		
Crude	Ref	0.309 (-0.231, 0.849)	0.137 (0.006, 0.267)	0.041	0.082
Model 1 ¹	Ref	0.252 (-0.252, 0.756)	0.111 (-0.011, 0.233)	0.077	0.154
Model 2 ²	Ref	0.306 (-0.195, 0.806)	0.121 (-0.000, 0.243)	0.052	0.108
Outcome	Low-Average	Good OR (95% CI)	Continuous OR (95% CI)	P-value	FDR ⁵
ADHD incident (No/Yes)					
n =	269	185	454		
Crude	Ref	2.030 (0.940, 4.490)	1.320 (1.080, 1.630)	0.009	0.036
Model 1 ¹	Ref	1.820 (0.820, 4.070)	1.270 (0.003, 1.580)	0.024	0.096
Model 2 ²	Ref	1.720 (0.760, 3.980)	1.240 (1.000, 1.570)	0.054	0.108

Abbreviations: ADHD: Attention-Deficit/Hyperactivity Disorder, CI: Confidence Interval, FDR: False

Discovery Rate, OR: Odds Ratio, SDQ: Strengths & Difficulties Questionnaire.

¹ Model 1: Adjusted for sex, age, outcome baseline measurement & RCT group.

² Model 2: Model 1 further adjusted for BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income, outcome baseline measurement & RCT group.

³ All models were estimated using generalized linear models (GLMs) with a Gaussian distribution (identity link) for all outcomes, except for ADHD incidence, which was modelled using a logistic link (logit).

⁴ Lower scores indicate better performance.

⁵ FDR for p-value.

Table 8 Longitudinal associations between Mediterranean diet adherence and cognitive outcomes

Mediterranean Diet Adherence by Categories					
Outcome	Low-Average	Good β (95% CI)	Continuous β (95% CI)	P-value	FDR ⁶
Alerting Network Score (ANT) (ms) ⁴					
n =	343	232	575		
Crude	Ref	-0.459 (-8.239, 7.320)	0.219 (-1.571, 2.008)	0.811	0.946
Model 1 ¹	Ref	-0.556 (-6.284, 5.172)	0.493 (-0.827, 1.813)	0.464	0.866
Model 2 ²	Ref	-0.490 (-6.232, 5.252)	0.456 (-0.868, 1.779)	0.500	0.812
Orienting Network Score (ANT) (ms) ⁴					
n =	342	232	574		
Crude	Ref	-2.496 (-10.342, 5.351)	0.223 (-1.584, 2.030)	0.809	0.946
Model 1 ¹	Ref	-1.771 (-7.330, 3.788)	-0.215 (-1.498, 1.067)	0.742	0.866
Model 2 ²	Ref	-1.857 (-7.461, 3.748)	-0.258 (-1.552, 1.037)	0.696	0.812
Executive Attention Score (ANT) (ms) ⁴					
n =	342	232	574		
Crude	Ref	3.878 (-2.773, 10.528)	-0.557 (-2.089, 0.975)	0.476	0.946
Model 1 ¹	Ref	-0.908 (-5.215, 3.400)	-0.479 (-1.469, 0.510)	0.343	0.866
Model 2 ²	Ref	-1.005 (-5.355, 3.344)	-0.537 (-1.537, 0.463)	0.293	0.812
Fluid Intelligence Score (PMA-R) ⁵					
n =	341	230	571		
Crude	Ref	-0.234 (-0.832, 0.364)	-0.084 (-0.221, 0.054)	0.233	0.946
Model 1 ¹	Ref	-0.095 (-0.661, 0.470)	-0.024 (-0.154, 0.106)	0.718	0.866
Model 2 ²	Ref	-0.102 (-0.674, 0.470)	-0.026 (-0.158, 0.106)	0.695	0.812
Working Memory Score (d'4) ⁵					
n =	336	226	562		
Crude	Ref	-0.050 (-0.303, 0.203)	0.009 (-0.049, 0.067)	0.758	0.946
Model 1 ¹	Ref	-0.082 (-0.282, 0.119)	0.002 (-0.044, 0.048)	0.939	0.939
Model 2 ²	Ref	-0.083 (-0.285, 0.120)	0.002 (-0.044, 0.049)	0.928	0.928
Emotion Recognition Task Score (ERT) ⁵					
n =	341	231	572		
Crude	Ref	-0.100 (-1.036, 0.836)	-0.002 (-0.217, 0.213)	0.982	0.982
Model 1 ¹	Ref	0.032 (-0.803, 0.866)	0.059 (-0.133, 0.251)	0.549	0.866
Model 2 ²	Ref	0.055 (-0.778, 0.889)	0.052 (-0.140, 0.244)	0.598	0.812
Advantageous Risk-Taking Score (Roulettes Task) ⁵					
n =	343	231	574		
Crude	Ref	0.108 (-0.344, 0.559)	0.025 (-0.079, 0.128)	0.643	0.946
Model 1 ¹	Ref	0.194 (-0.186, 0.575)	0.056 (-0.031, 0.144)	0.207	0.866
Model 2 ²	Ref	0.169 (-0.208, 0.547)	0.042 (-0.045, 0.129)	0.343	0.812

Abbreviations: ANT: Attentional Network Test, CI: Confidence Interval, FDR: False Discovery Rate, PMA-R: Primary Mental Abilities-Revised.

¹ Model 1: Adjusted for sex, age, outcome baseline measurement & RCT group.

² Model 2: Model 1 further adjusted for BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income, outcome baseline measurement & RCT group.

³ All models were estimated using generalized linear models (GLMs) with Gaussian (identity) distribution for all outcomes.

⁴ Lower scores indicate better performance.

⁵ Higher scores indicate better performance.

⁶ FDR for p-value.

In contrast, high vs. low UPF intake tertile was longitudinally associated with increased internalising problems (Model 2: $\beta = 0.524$; 95% CI: 0.015, 1.034; P-trend = 0.042; **Table 9**) and with poorer performance in advantageous risk-taking decisions (Model 2: $\beta = -0.533$; 95% CI: -0.985, -0.081; P-trend = 0.022; **Table 10**). However, no association survived FDR correction. No significant associations were found between UPF intake and other behavioural, mental health, or cognitive outcomes.

Table 9 Longitudinal associations between ultra-processed food consumption and behavioural and mental health outcomes

Ultra-Processed Food Consumption by Tertiles								
Outcome	Low	Moderate β (95% CI)	High β (95% CI)	P-trend	FDR ³	Continuous β (95% CI)	P-value	FDR ⁴
Total Behavioural Difficulties Score (SDQ) ⁶								
n =	116	110	101			327		
Crude	Ref	0.289 (-0.677, 1.255)	0.247 (-0.743, 1.237)	0.613	0.759	0.001 (-0.052, 0.054)	0.983	0.983
Model 1 ¹	Ref	0.527 (-0.365, 1.419)	0.850 (-0.069, 1.769)	0.068	0.136	0.031 (-0.018, 0.080)	0.221	0.409
Model 2 ²	Ref	0.649 (-0.238, 1.535)	0.761 (-0.148, 1.670)	0.095	0.190	0.024 (-0.025, 0.073)	0.344	0.473
Internalising Problems Score (SDQ) ⁶								
n =	116	110	101			327		
Crude	Ref	0.090 (-0.492, 0.672)	0.151 (-0.445, 0.748)	0.617	0.759	-0.003 (-0.035, 0.029)	0.869	0.983
Model 1 ¹	Ref	0.258 (-0.246, 0.762)	0.531 (0.013, 1.049)	0.045	0.136	0.016 (-0.012, 0.043)	0.271	0.409
Model 2 ²	Ref	0.358 (-0.140, 0.856)	0.524 (0.015, 1.034)	0.042	0.168	0.013 (-0.014, 0.041)	0.345	0.473
Externalising Problems Score (SDQ) ⁶								
n =	116	110	101			327		
Crude	Ref	0.199 (-0.446, 0.845)	0.096 (-0.566, 0.757)	0.759	0.759	0.003 (-0.032, 0.039)	0.857	0.983
Model 1 ¹	Ref	0.288 (-0.313, 0.890)	0.365 (-0.253, 0.983)	0.239	0.319	0.017 (-0.016, 0.050)	0.307	0.409
Model 2 ²	Ref	0.306 (-0.301, 0.913)	0.269 (-0.350, 0.889)	0.379	0.379	0.012 (-0.021, 0.046)	0.473	0.473
Outcome	Low	Moderate OR (95% CI)	High OR (95% CI)	P-trend	FDR ³	Continuous OR (95% CI)	P-value	FDR ⁴
ADHD incident (No/Yes)								
n =	155	156	143			454		
Crude	Ref	0.443 (0.152, 1.150)	0.744 (0.298, 1.780)	0.451	0.759	0.991 (0.937, 1.040)	0.748	0.983
Model 1 ¹	Ref	0.430 (0.146, 1.130)	0.686 (0.271, 1.660)	0.365	0.365	0.987 (0.932, 1.040)	0.633	0.633
Model 2 ²	Ref	0.370 (0.122, 1.010)	0.583 (0.218, 1.490)	0.222	0.296	0.979 (0.921, 1.030)	0.457	0.473

Abbreviations: ADHD: Attention-Deficit/Hyperactivity Disorder, CI: Confidence Interval, FDR: False Discovery Rate, OR: Odds Ratio,

SDQ: Strengths & Difficulties Questionnaire.

¹ Model 1: Adjusted for sex, age, outcome baseline measurement & RCT group.

² Model 2: Model 1 further adjusted for BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income, maternal mental health disorder, outcome baseline measurement & RCT group.

³ FDR for p-trend value.

⁴ FDR for p-value.

⁵ All models were estimated using generalized linear models (GLMs) with a Gaussian distribution (identity link) for all outcomes, except for ADHD incidence, which was modelled using a logistic link (logit).

⁶ Lower scores indicate better performance.

Table 10 Longitudinal associations between ultra-processed food consumption and cognitive outcomes

Ultra-Processed Food Consumption by Tertiles								
Outcome	Low	Moderate β (95% CI)	High β (95% CI)	P-trend	FDR ³	Continuous β (95% CI)	P-value	FDR ⁴
Alerting Network Score (ANT) (ms) ⁶								
n =	199	188	188			575		
Crude	Ref	0.923 (-8.392, 10.237)	0.042 (-9.273, 9.356)	0.990	0.990	-0.058 (-0.537, 0.421)	0.813	0.820
Model 1 ¹	Ref	-1.234 (-8.030, 5.562)	2.188 (-4.609, 8.986)	0.539	0.663	0.102 (-0.250, 0.454)	0.570	0.797
Model 2 ²	Ref	-1.278 (-8.075, 5.518)	2.292 (-4.606, 9.190)	0.533	0.644	0.149 (-0.211, 0.510)	0.417	0.730
Orienting Network Score (ANT) (ms) ⁶								
n =	199	188	187			574		
Crude	Ref	1.623 (-7.767, 11.014)	-1.068 (-10.472, 8.335)	0.831	0.990	-0.293 (-0.776, 0.189)	0.234	0.474
Model 1 ¹	Ref	-2.170 (-8.770, 4.430)	-1.890 (-8.496, 4.715)	0.569	0.663	-0.177 (-0.518, 0.164)	0.310	0.723
Model 2 ²	Ref	-1.927 (-8.566, 4.713)	-1.540 (-8.283, 5.204)	0.644	0.644	-0.160 (-0.512, 0.192)	0.374	0.730
Executive Attention Score (ANT) (ms) ⁶								
n =	198	188	188			574		
Crude	Ref	0.157 (-7.775, 8.089)	5.456 (-2.476, 13.388)	0.181	0.453	0.139 (-0.269, 0.547)	0.504	0.701
Model 1 ¹	Ref	2.451 (-2.636, 7.538)	3.945 (-1.142, 9.032)	0.128	0.448	0.137 (-0.126, 0.400)	0.307	0.723
Model 2 ²	Ref	2.317 (-2.810, 7.445)	3.979 (-1.225, 9.183)	0.133	0.466	0.138 (-0.134, 0.410)	0.320	0.730
Fluid Intelligence Score (PMA-R) ⁷								
n =	196	187	188			571		
Crude	Ref	-0.352 (-1.070, 0.366)	-0.101 (-0.818, 0.617)	0.775	0.990	-0.004 (-0.041, 0.033)	0.820	0.820
Model 1 ¹	Ref	-0.309 (-0.980, 0.362)	-0.222 (-0.892, 0.448)	0.509	0.663	-0.012 (-0.047, 0.022)	0.486	0.797
Model 2 ²	Ref	-0.319 (-0.995, 0.358)	-0.170 (-0.856, 0.515)	0.609	0.644	-0.008 (-0.043, 0.028)	0.678	0.826
Working Memory Score (d'4) ⁷								
n =	195	185	182			562		
Crude	Ref	-0.148 (-0.448, 0.152)	-0.026 (-0.327, 0.276)	0.852	0.990	0.009 (-0.007, 0.024)	0.271	0.474
Model 1 ¹	Ref	-0.249 (-0.486, -0.012)	-0.140 (-0.378, 0.098)	0.236	0.551	0.002 (-0.010, 0.014)	0.744	0.868
Model 2 ²	Ref	-0.245 (-0.484, -0.006)	-0.149 (-0.393, 0.094)	0.208	0.485	0.001 (-0.012, 0.014)	0.885	0.885
Emotion Recognition Task Score (ERT) ⁷								
n =	198	188	186			572		
Crude	Ref	0.407 (-0.708, 1.522)	0.864 (-0.254, 1.982)	0.130	0.453	0.045 (-0.013, 0.102)	0.131	0.459
Model 1 ¹	Ref	0.407 (-0.581, 1.395)	0.185 (-0.811, 1.181)	0.701	0.701	0.004 (-0.048, 0.056)	0.872	0.872
Model 2 ²	Ref	0.391 (-0.593, 1.374)	0.314 (-0.688, 1.316)	0.525	0.644	0.010 (-0.043, 0.063)	0.708	0.826
Advantageous Risk-Taking Score (Roulettes Task) ⁷								
n =	198	188	188			574		
Crude	Ref	0.114 (-0.423, 0.652)	-0.362 (-0.899, 0.175)	0.194	0.453	-0.022 (-0.049, 0.006)	0.126	0.459
Model 1 ¹	Ref	-0.104 (-0.553, 0.345)	-0.625 (-1.075, -0.175)	0.007	0.049	-0.029 (-0.052, -0.006)	0.015	0.105
Model 2 ²	Ref	-0.140 (-0.586, 0.305)	-0.533 (-0.985, -0.081)	0.022	0.154	-0.021 (-0.045, 0.003)	0.082	0.574

Abbreviations: ANT: Attentional Network Test, CI: Confidence Interval, FDR: False Discovery Rate, PMA-R: Primary Mental Abilities–Revised.

¹ Model 1: Adjusted for sex, age, outcome baseline measurement & RCT group.

² Model 2: Model 1 further adjusted for BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income, maternal mental health disorder, outcome baseline measurement & RCT group.

³ FDR for p-trend value.

⁴ FDR for p-value.

⁵ All models were estimated using generalized linear models (GLMs) with Gaussian (identity) distribution for all outcomes.

⁶ Lower scores indicate better performance.

⁷ Higher scores indicate better performance.

Biomarker Signature Development

A UPF-related biomarker signature was successfully developed using the elastic net regression approach described in the methods. Fatty acid signatures for both UPF and MD dietary patterns were also constructed using the same method. UPF intake remained stable between baseline and follow-up (baseline: $13.22 \pm 7.65\%$; follow-up: $13.58 \pm 9.47\%$; Wilcoxon signed-rank test: $V = 28211$, $P = 0.473$, $n = 328$), whereas MD adherence (KIDMED scores) changed significantly over time (baseline: 7.00 ± 2.06 ; follow-up: 7.32 ± 2.14 ; $V = 11675$, $P = 0.0027$, $n = 320$).

Although, in principle, four biomarker signatures could have been constructed (fatty acid and polyphenol signatures for both UPF and MD), only three were ultimately developed. This is because urinary polyphenols were only measured at follow-up, so any polyphenol signature would necessarily reflect dietary patterns at that time point rather than at baseline.

For UPF, this is methodologically acceptable, as UPF intake did not change significantly over time and follow-up values can reasonably represent habitual intake. In contrast, since MD adherence changed significantly between baseline and follow-up, it would be methodologically unsound to assume that MD status at follow-up reflects baseline status; thus, constructing a polyphenol signature for MD was not appropriate. By comparison, both dietary exposures (UPF and MD) and RBC membrane fatty acids were measured at baseline, allowing for the development of fatty acid signatures for both dietary patterns.

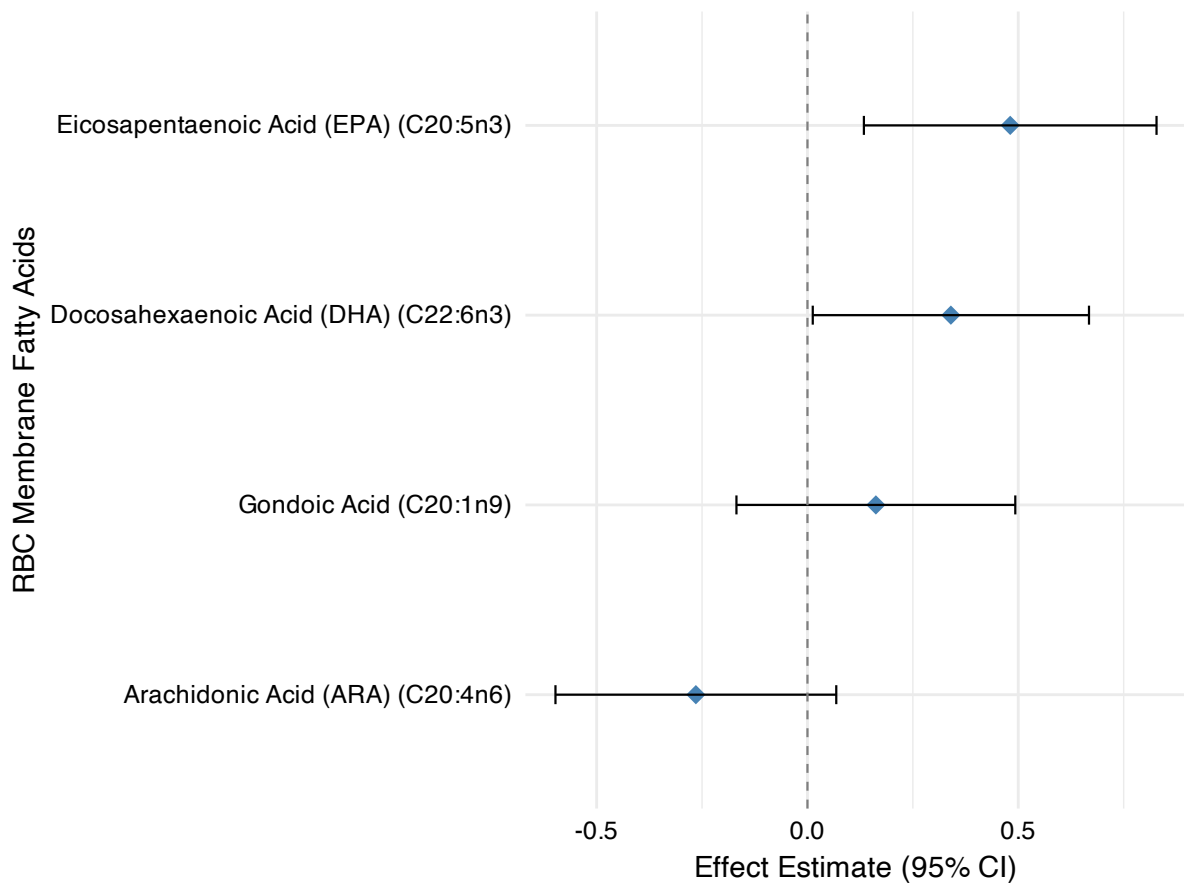
Fatty Acid Signature of MD Adherence

Four RBC membrane fatty acids formed a biomarker signature for MD adherence based on consistent associations (**Table 13**). The model explained approximately 4.7% of the variance in KIDMED scores ($R^2 = 0.047$; 95% CI: 0.011, 0.106), with a Pearson correlation of 0.22 (95% CI: 0.10, 0.33).

Table 11 Bootstrap estimates of model performance for the RBC membrane fatty acid signature of Mediterranean Diet adherence

Metric	Estimate	Lower CI	Upper CI
R ²	0.046617	0.010546	0.106243
Pearson Correlation	0.215911	0.102695	0.325949

Four RBC membrane fatty acids were included in the signature: Gondoic Acid (C20:1n9), Arachidonic Acid (ARA) (C20:4n6), Eicosapentaenoic Acid (EPA) (C20:5n3), and Docosahexaenoic Acid (DHA) (C22:6n3). Their model¹ coefficients and 95% confidence intervals are presented in **Figure 5**.



¹ Model: Elastic net regression. Exposure: RBC membrane fatty acids (n = 23, standardised). Outcome: Mediterranean Diet.

Figure 3 Associations between individual RBC membrane fatty acids and MD adherence. Effect estimates and 95% confidence intervals are shown for each fatty acids included in the biomarker signature model.

Polyphenol Signature of UPF Consumption

Thirteen urinary polyphenols formed a biomarker signature for UPF intake based on consistent associations (**Table 11**). The model explained 13% of UPF intake variance ($R^2 = 0.13$; 95% CI: 0.06, 0.21), with a Pearson correlation of 0.36 (95% CI: 0.25, 0.46).

Table 12 Bootstrap estimates of model performance for the metabolic urinary polyphenol signature of ultra-processed food consumption

Metric	Estimate	Lower CI	Upper CI
R^2	0.128186	0.062190	0.211357
Pearson Correlation	0.358031	0.249379	0.459736

Six metabolites showed positive associations (protocatechuic acid glucuronide, ferulic acid sulphate, homovanillic acid glucuronide, dihydrocaffeic acid glucuronide, dihydrocaffeic/homovanillic sulphate and 4-hydroxybenzoic acid), while seven showed negative associations (ferulic acid glucuronide, coumaric acid glucuronide, syringic acid, syringic acid sulphate, catechol sulphate, enterolactone glucuronide and sinapic acid sulphate). Model² coefficients are in **Figure 3**.

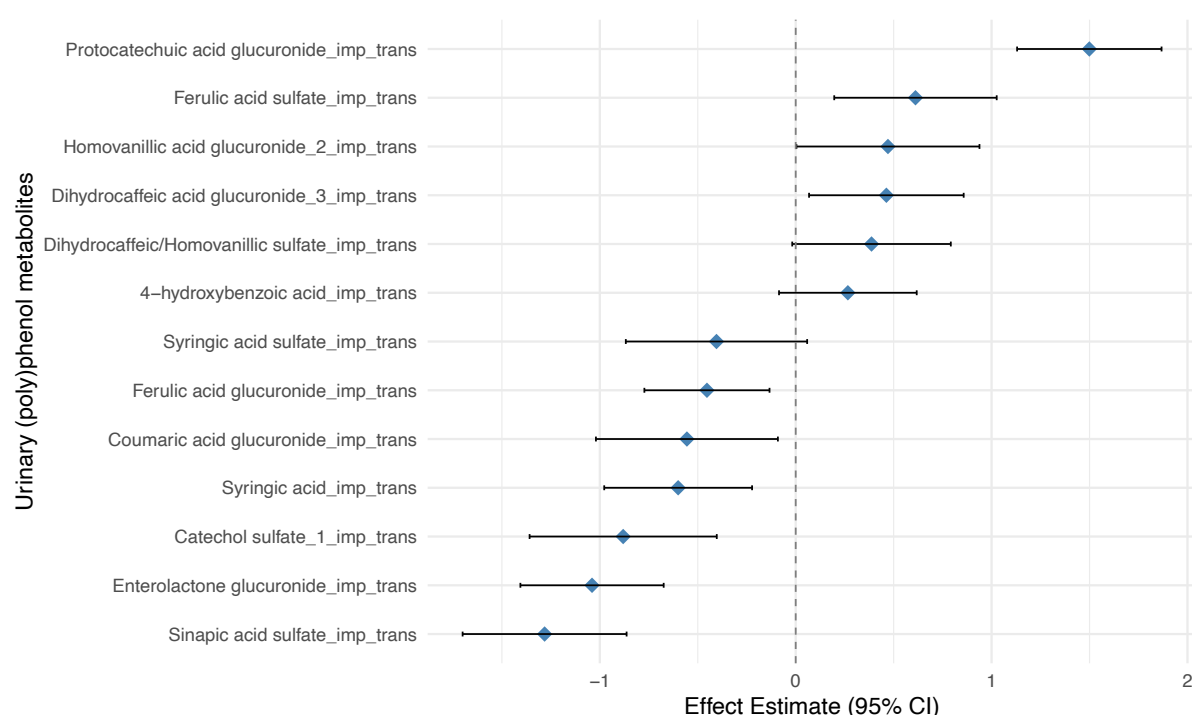


Figure 4. Associations between individual urinary polyphenol metabolites and UPF consumption. Effect estimates and 95% confidence intervals are shown for each metabolite included in the biomarker signature model.

² Model: Elastic net regression. Exposure: urinary polyphenol metabolites (n = 13, imputed and inverse-normal transformed). Outcome: ultra-processed food consumption (residuals after regressing on intervention group).

Fatty Acid Signature of UPF Consumption

Two RBC membrane fatty acids formed a biomarker signature for UPF consumption based on consistent associations (**Table 12**). The model explained approximately 4% of UPF consumption variance ($R^2 = 0.039$; 95% CI: 0.004, 0.106), with a Pearson correlation of 0.20 (95% CI: 0.06, 0.33).

Table 13 Bootstrap estimates of model performance for the RBC membrane fatty acid signature of ultra-processed food consumption

Metric	Estimate	Lower CI	Upper CI
R^2	0.038708	0.003700	0.106488
Pearson Correlation	0.196744	0.060825	0.326324

Two RBC membrane fatty acids showed associations with UPF intake. Linoleic acid (C18:2n6) demonstrated a positive association with UPF consumption, while elaidic acid (C18:1n9-trans) showed a negative association. These fatty acids formed the signature of UPF consumption, with model³ coefficients and their 95% confidence intervals displayed in **Figure 4**.

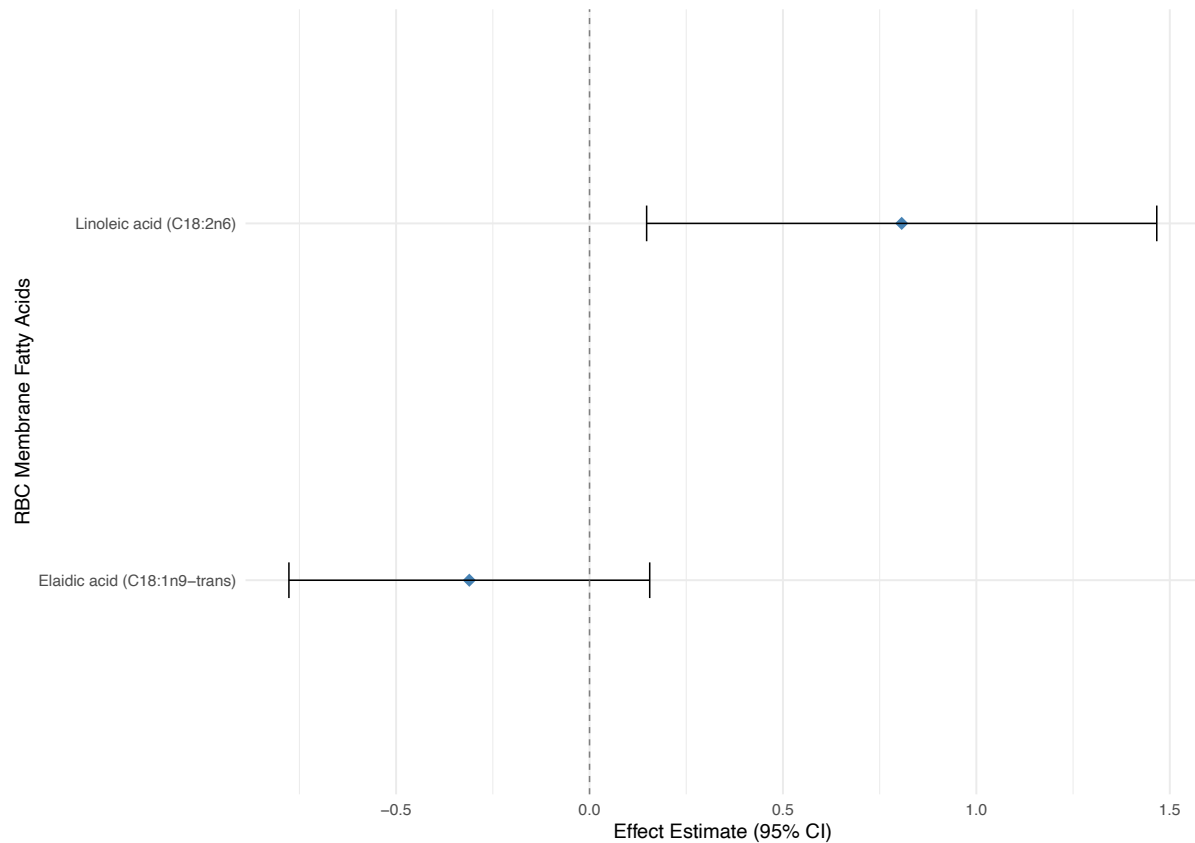


Figure 5. Associations between individual RBC membrane fatty acids and UPF consumption. Effect estimates and 95% confidence intervals are shown for each fatty acids included in the biomarker signature model.

³ Model: Elastic net regression. Exposure: RBC membrane fatty acids (n = 23, standardised). Outcome: ultra-processed food consumption.

Associations and Mediation Analyses of Individual Biomarkers and Biomarker Signatures

Mediation Analysis Using Meet-in-the-Middle Approach

After applying the meet-in-the-middle approach, no individual biomarker was found to mediate the relationship between the *MD* or *UPF consumption* and neuropsychological outcomes, with all mediation analyses yielding non-significant results (all p-values > 0.05).

Biomarker Signature Associations and Mediation Analysis

Cross-sectional and longitudinal GLM analyses were performed to assess associations between UPF-related biomarker signatures (fatty acid and polyphenol) and neuropsychological outcomes. No significant associations were observed for either signature (all p-values > 0.05). In contrast, the MD fatty acid signature was significantly associated with neuropsychological outcomes in both cross-sectional and longitudinal analyses after covariate adjustment.

Cross-sectionally, in model 2, a higher MD fatty acid signature was associated with lower Total Behavioural Difficulties ($\beta = -0.572$; 95% CI: $-1.090, -0.050$; $P = 0.033$, FDR = 0.066), although this association did not remain significant after FDR correction (**Table 14**). A higher MD fatty acid signature was also inversely associated with odds of ADHD symptoms diagnosis (OR = -0.948 ; 95% CI: $-1.670, -0.314$; $P = 0.006$, FDR = 0.024), and this association persisted after FDR correction in both model 1 and model 2. No significant associations were observed for internalising or externalising problems.

Table 14 Cross-sectional associations between Mediterranean Diet RBC membrane fatty acid signature and behavioural and mental health outcomes

Outcome	Continuous β (95% CI)	P-value	FDR
Total Behavioural Difficulties Score (SDQ) ⁴ n = 301			
Model 1 ¹	-0.495 (-1.020, 0.027)	0.064	0.128
Model 2 ²	-0.572 (-1.090, -0.050)	0.033	0.066
Internalising Problems Score (SDQ) ⁴ n = 301			
Model 1 ¹	-0.222 (-0.504, 0.060)	0.120	0.160
Model 2 ²	-0.278 (-0.563, 0.007)	0.057	0.076
Externalising Problems Score (SDQ) ⁴ n = 301			
Model 1 ¹	-0.273 (-0.657, 0.111)	0.200	0.200
Model 2 ²	-0.293 (-0.675, 0.089)	0.130	0.130
Outcome	Continuous OR (95% CI)	P-value	FDR
ADHD symptoms diagnosis (No/Yes) n = 276			
Model 1 ¹	-0.948 (-1.670, -0.313)	0.006	0.024
Model 2 ²	-0.948 (-1.670, -0.314)	0.006	0.024

Abbreviations: ADHD: Attention-Deficit/Hyperactivity Disorder, CI: Confidence Interval, FDR: False Discovery Rate, OR: Odds Ratio, SDQ: Strengths & Difficulties Questionnaire.

¹ Adjusted for sex, age, BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income & MD adherence (continuous).

² Adjusted for sex, age, BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income & MD adherence (categorical).

³ All models were estimated using generalized linear models with appropriate family distributions: Gaussian (identity) for internalising problems, externalising problems and behavioural problems; and logistic regression (binomial) for ADHD.

⁴ Lower scores indicate better performance.

Longitudinally, a higher MD RBC fatty acid signature score was significantly associated with increased Internalising Problems Scores in both Model 1 ($\beta = 0.366$, 95% CI: 0.033–0.699, $p = 0.033$, FDR = 0.132) and Model 2 ($\beta = 0.376$, 95% CI: 0.044–0.709, $p = 0.028$, FDR = 0.112); however, these associations did not remain significant after FDR correction (**Table 15**). No other significant associations were found.

Table 15 Longitudinal associations between Mediterranean Diet RBC membrane fatty acid signature and behavioural and mental health outcomes

Outcome	Continuous β (95% CI)	P-value	FDR
Total Behavioural Difficulties Score (SDQ) ⁴ n = 169			
Model 1 ¹	0.397 (−0.222, 1.015)	0.211	0.281
Model 2 ²	0.434 (−0.185, 1.053)	0.172	0.229
Internalising Problems Score (SDQ) ⁴ n = 169			
Model 1 ¹	0.366 (0.033, 0.699)	0.033	0.132
Model 2 ²	0.376 (0.044, 0.709)	0.028	0.112
Externalising Problems Score (SDQ) ⁴ n = 169			
Model 1 ¹	0.012 (−0.417, 0.441)	0.955	0.955
Model 2 ²	0.037 (−0.394, 0.468)	0.867	0.867
Outcome	Continuous OR (95% CI)	P-value	FDR
ADHD incident (No/Yes) n = 200			
Model 1 ¹	0.585 (0.302, 1.058)	0.091	0.182
Model 2 ²	0.648 (0.344, 1.147)	0.154	0.229

Abbreviations: ADHD: Attention-Deficit/Hyperactivity Disorder, CI: Confidence Interval, FDR: False Discovery Rate, OR: Odds Ratio, SDQ: Strengths & Difficulties Questionnaire.

¹ Adjusted for sex, age, BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income, outcome baseline measurement (except for ADHD incident) & RCT group & MD adherence (continuous).

² Adjusted for sex, age, BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income, outcome baseline measurement (except for ADHD incident) & RCT group & MD adherence (categorical).

³ All models were estimated using generalized linear models with a Gaussian distribution (identity link) for all outcomes, except for ADHD incidence, which was modelled using a logistic link (logit).

⁴ Lower scores indicate better performance.

As shown in **Table 16**, a higher MD RBC fatty acid signature in model 2 was associated with better performance on the Alerting Network ($\beta = -5.081$, 95% CI: −9.292 to −0.871, $p = 0.019$; FDR = 0.066) and Executive Attention ($\beta = -3.689$, 95% CI: −6.635 to −0.744, $p = 0.015$; FDR = 0.066); however, these associations did not remain significant after FDR correction. Similar results were observed in model 1. No other significant associations were found.

Table 16 Longitudinal associations between Mediterranean Diet RBC membrane fatty acid signature and cognitive outcomes

Outcome	Continuous β (95% CI)	P-value	FDR
Alerting Network Score (ANT) (ms) ⁴			
n =281			
Model 1 ¹	-4.616 (-8.800, -0.432)	0.031	0.110
Model 2 ²	-5.081 (-9.292, -0.871)	0.019	0.066
Orienting Network Score (ANT) (ms) ⁴			
n =281			
Model 1 ¹	-1.471 (-5.658, 2.717)	0.492	0.861
Model 2 ²	-1.471 (-5.687, 2.744)	0.495	0.792
Executive Attention Score (ANT) (ms) ⁴			
n =280			
Model 1 ¹	-3.601 (-6.523, -0.679)	0.016	0.110
Model 2 ²	-3.689 (-6.635, -0.744)	0.015	0.066
Fluid Intelligence Score (PMA-R) ⁵			
n =279			
Model 1 ¹	0.026 (-0.414, 0.465)	0.908	0.908
Model 2 ²	0.071 (-0.370, 0.512)	0.753	0.792
Working Memory Score (d'4) ⁵			
n =274			
Model 1 ¹	0.033 (-0.113, 0.179)	0.661	0.908
Model 2 ²	0.042 (-0.105, 0.189)	0.577	0.792
Emotion Recognition Task Score (ERT) ⁵			
n =280			
Model 1 ¹	0.072 (-0.577, 0.720)	0.829	0.908
Model 2 ²	0.088 (-0.565, 0.741)	0.792	0.792
Advantageous Risk-Taking Score (Roulettes Task) ⁵			
n =280			
Model 1 ¹	-0.107 (-0.390, 0.176)	0.460	0.861
Model 2 ²	-0.106 (-0.391, 0.179)	0.467	0.792

Abbreviations: ANT: Attentional Network Test, CI: Confidence Interval, FDR: False Discovery Rate, PMA-R: Primary Mental Abilities-Revised.

¹ Adjusted for sex, age, BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income, baseline measurement of the outcome, RCT group & MD adherence (continuous).

² Adjusted for sex, age, BMI, ethnicity, substance use, maternal educational attainment, physical activity, annual net household income, outcome baseline measurement, RCT group & MD adherence (categorical).

³ All models were estimated using generalized linear models with Gaussian (identity) distribution for all outcomes.

⁴ Lower scores indicate better performance.

⁵ Higher scores indicate better performance.

In mediation analysis (**Table 17**), only the indirect effect (ACME) of the MD fatty acids signature on ADHD was significant (ACME = -0.005, 95% CI: -0.009 to -0.001, $p = 0.009$). Neither the direct effect (ADE) nor the total effect were significant.

Table 17 *Causal Mediation Analysis of the Mediterranean Diet Fatty Acid Signature on ADHD*

Effect	Estimate	95% CI Lower	95% CI Upper	P-value
ACME (indirect)	-0.005	-0.009	-0.001	0.009
ADE (direct)	0.009	-0.013	0.030	0.418
Total Effect	0.004	-0.016	0.024	0.719
Proportion Mediated	-1.334	-7.058	7.116	0.713

ACME: Average Causal Mediation Effect; ADE: Average Direct Effect.

Sample size: 276; Bootstrap simulations: 10,000.

Discussion

This study is the first to concurrently examine both adherence to the MD and UPF consumption, cross-sectionally and longitudinally, in relation to a wide range of neuropsychological outcomes in adolescents. Higher adherence to the MD was associated with better executive function and fewer behavioural problems, including internalising and externalising symptoms, with these associations persisting after correction for multiple comparisons. In contrast, higher UPF intake was associated with increased behavioural problems, internalising symptoms, impaired advantageous risk-taking decisions, borderline ADHD symptom diagnoses, poorer alerting network performance, and reduced emotion recognition, with the latter remaining significant after correction for multiple comparisons. Longitudinally, higher UPF intake was associated with impaired advantageous risk-taking decisions and increased internalising problems, whereas no longitudinal associations were found for MD adherence.

Biomarker mediation analyses indicated that neither individual polyphenols nor fatty acids mediated the relationship between dietary patterns and neuropsychological outcomes. Composite biomarker signatures for UPF were also not significantly associated with outcomes. However, the MD fatty acid signature was cross-sectionally associated with lower behavioural difficulties, but this association did not remain significant after FDR correction. In contrast, the association with reduced odds of ADHD symptoms diagnosis remained significant after FDR correction. Longitudinally, the MD fatty acid signature was initially associated with better executive function, improved alerting performance, and higher internalising symptoms; however, none of these longitudinal associations remained significant after correction for multiple comparisons. Mediation analysis suggested only a modest indirect pathway between MD adherence and ADHD via the MD-fatty acid signature.

These findings indicate that greater adherence to an MD pattern is associated with improved behavioural and cognitive outcomes, whereas higher UPF consumption is negatively associated with multiple neuropsychological domains in adolescents. However, the scarcity of longitudinal associations points to complex and potentially transient relationships, underscoring the need for further research. The results also emphasise the importance of promoting healthy dietary habits during adolescence, while highlighting the ongoing challenge of identifying robust biomarker-based mechanisms linking diet to neuropsychological outcomes.

In the present sample, a considerable proportion of adolescents reported high adherence to the MD (39.9%), a prevalence comparable to previous reports among Spanish youth and slightly higher than recent national estimates (Herrera-Ramos et al. 2023). This relatively high adherence may be partly explained by higher maternal education, consistent with prior studies linking parental education to healthier dietary patterns (Arcila-Agudelo et al. 2019; Herrera-Ramos et al. 2023; Rito et al. 2019).

Cross-sectionally, higher MD adherence was associated with fewer behavioural problems in adolescents. These findings are consistent with several recent studies from Spain demonstrating that greater adherence to the MD is linked to lower odds of depressive symptoms (Jiménez-López et al. 2024), better psychosocial health, and fewer conduct and hyperactivity problems (Alfaro-González et al. 2023), as well as more favourable behavioural and cognitive profiles (O’Neil et al. 2014). Similarly, (Esteban-Gonzalo et al. 2019) observed consistent associations between MD adherence and enhanced well-being in youth.

In relation to cognitive performance, higher MD adherence was linked to higher executive attention, partially aligning with the HELENA study, which found better attention capacity associated with overall diet quality, though not specifically with MD adherence (Henriksson et al. 2017). No significant associations were observed with MD adherence and working memory or fluid intelligence. In contrast, among Chilean adolescents adhering to a Mediterranean-style dietary pattern was associated with better working memory and cognitive flexibility, although no significant differences were found in fluid intelligence (Peña-Jorquera et al. 2024).

Longitudinal analyses did not reveal associations between baseline MD adherence and subsequent cognitive, behavioural, or mental health outcomes. This lack of longitudinal association is consistent with previous work showing no long-term effect of MD adherence on well-being in adolescents (Esteban-Gonzalo et al. 2019). These results suggest that the neuropsychological benefits of MD adherence in adolescence may be limited to the time of exposure, rather than persisting over time. The absence of consistent longitudinal associations may be attributable to the rapid and non-linear brain development characteristic of adolescence, which could attenuate or obscure longer-term dietary effects (Hooper et al. 2004; Leon-Carrion, García-Orza, and Pérez-Santamaría 2004; Luciana et al. 2005; Luna et al. 2004; McGivern et al. 2002).

In secondary analyses using biomarker signatures, the MD fatty acid signature was cross-sectionally associated with fewer behavioural difficulties, reinforcing the primary

findings. Additionally, these analyses extended the main results by revealing reduced odds of ADHD symptoms diagnosis cross-sectionally, a relationship that was mediated through the MD fatty acid signature and positively linked to omega-3 fatty acids (EPA & DHA). Mediation analysis indicated a significant indirect effect of the MD fatty acid signature on ADHD risk, which aligns with previous literature suggesting that antioxidant and anti-inflammatory dietary components may help prevent neurodevelopmental disorders (Turiaco et al. 2024). Supporting evidence includes reports of lower RBC DHA and higher trans-fatty acids in children with ADHD (Armon-Omer et al. 2021).

Longitudinal associations, such as improved alerting network performance and executive function, were not identified in the main analysis but did emerge in the biomarker subsample. This supports previous findings that higher RBC DHA is related to better attention (Pinar-Martí et al. 2022). Notably, executive function was cross-sectionally associated with MD adherence in the primary analysis, and this association extended longitudinally when considering the fatty acid signature. An unexpected longitudinal association between the MD fatty acid signature and increased internalising symptoms was also observed in the biomarker subsample; however, since this result was not FDR significant, it is likely attributable to chance or the reduced sample size. Overall, only the ADHD finding remained FDR significant, so all other results, especially those from secondary analyses with a substantially reduced sample, should be interpreted with caution.

The mean UPF intake (%UPF = 13.6% of total grams/d) in this sample was consistent with previous studies in European adolescents and adults (Borloz et al. 2021; Huybrechts et al. 2022), and recent data indicate a potential increase in UPF consumption over time, with marked regional variation (Chavez-Ugalde et al. 2024; Monteiro et al. 2017).

Cross-sectionally, higher UPF intake was associated with more behavioural difficulties and internalising problems, but not with ADHD symptoms. These findings align with prior studies and meta-analyses documenting greater internalising symptoms, depression, and psychosocial impairment with higher UPF consumption (Jacka et al. 2011, 2013; Orlando et al. 2022; Reales-Moreno et al. 2022). Higher UPF intake was also linked to poorer alerting network performance, impaired emotion recognition, and reduced advantageous risk-taking, which represents a novel contribution to the literature on diet and adolescent cognitive function. No associations were observed between UPF intake and working memory or fluid intelligence, a finding consistent with previous research (dos Santos et al. 2024).

Longitudinal analyses revealed that higher baseline UPF consumption was associated with increased internalising problems and impaired advantageous risk-taking, corroborating evidence from prospective studies and meta-analyses for internalising symptoms (Jacka et al. 2011, 2013; Orlando et al. 2022).

Secondary analyses of biomarker signatures did not identify significant associations between UPF-related polyphenol or fatty acid signatures and neuropsychological outcomes.

The MD supports neurodevelopment through several complementary mechanisms. Omega-3 fatty acids, especially DHA, enhance neuroplasticity, membrane fluidity, and the production of brain-derived neurotrophic factor, contributing to optimal synaptic function and resilience (Gómez-Pinilla and Gómez 2008). Polyphenols in the diet exert anti-inflammatory effects and help regulate neurotransmitter balance (Hunt, Pontifex, and Vauzour 2024; Tavan et al. 2023; Vauzour et al. 2010), while a rich supply of vitamins and minerals promotes brain connectivity and structural maturation (Dyall 2015). The association between the MD fatty acid signature and reduced ADHD risk aligns with the hypothesis that antioxidant and healthy fat-rich dietary patterns may modulate neuroinflammatory and oxidative stress pathways, supporting neurodevelopment and protecting against neurodevelopmental disorders (Gómez-Pinilla and Gómez 2008; Turiaco et al. 2024).

UPFs can negatively impact neural function through diverse pathways. Ingredients typical of UPFs, such as added sugars, trans fats, emulsifiers, and preservatives—can disrupt gut barrier integrity, increase endotoxin translocation, and trigger neuroinflammation via cytokines like IL-1 β and TNF- α (Cryan and Dinan 2012; Morais, Schreiber, and Mazmanian 2020; Reichelt et al. 2017). This inflammatory environment impairs dopaminergic and serotonergic signalling, essential for emotional regulation and executive function (Miller and Raison 2015; Volkow et al. 2007), and may alter blood-brain barrier permeability, potentially affecting emotion identification and cognitive processing (Falkenstein et al. 2024). The hyper-palatable nature and poor nutritional profile of UPFs are further linked to reduced intake of essential nutrients, diminished synaptic plasticity, and compromised PFC function (Arnsten 2009; Gómez-Donoso et al. 2020; Morin et al. 2017; Pursey, Davis, and Burrows 2017; Victoria J. Drake 2011).

In addition to these mechanisms, urinary polyphenols associated with UPF consumption in adolescents were investigated, an area that remains relatively unexplored (Muli et al. 2024). UPF intake was positively associated with protocatechuic acid glucuronide, likely derived from food colourants (Aguilar et al. 2013; Kiriya et al. 2024; Olivas-Aguirre et al.

2016) and ferulic acid sulphate, a compound with increased bioavailability from cereal processing (Manach et al. 2004; Muli et al. 2024; Runge-Morris and Kocarek 2009). Other preservative-related compounds such as homovanillic acid glucuronide (Chassaing et al. 2015; Guo et al. 2021; Schulte, Avena, and Gearhardt 2015; Zinöcker and Lindseth 2018), dihydrocaffeic acid glucuronide (Neveu et al. 2010; Olthof, Hollman, and Katan 2001; PhytoHub: n.d.), and 4-hydroxybenzoic acid (Olivas-Aguirre et al. 2016; Soni, Carabin, and Burdock 2005) were also associated with higher UPF intake.

Conversely, several polyphenol metabolites and plant-derived compounds were inversely associated with UPF intake, including ferulic acid glucuronide, syringic acid and its sulphate, coumaric acid glucuronide, sinapic acid sulphate, and enterolactone glucuronide, biomarkers of whole grains and minimally processed foods (Boronat et al. 2021; Chemical Aging 2012; (Regulation (EC) No 1334/2008, 2008).; Li et al. 2024; Lončar et al. 2020; Manach et al. 2004; Mithul Aravind et al. 2021). Enterolactone glucuronide is a known marker of fibre-rich diets (Boronat et al. 2021), while sulphate, probably derived from plant foods (Kim et al. 2022; Pimpão et al. 2015; Wu et al. 2014) and benzoate preservatives (Muli et al. 2024), and syringic and sinapic acid derivatives (Chemical Aging 2012; Mithul Aravind et al. 2021; Srinivasulu et al. 2018) were all inversely related to UPF intake.

To complement polyphenol biomarker analysis, the study investigated red blood cell (RBC) membrane fatty acids as potential biomarkers of UPF consumption. Two fatty acids showed significant associations with UPF intake. Linoleic acid (C18:2n6) was positively associated with UPF intake, consistent with evidence that UPF consumption correlates with omega-6 fatty acid intake from vegetable oils commonly used in food processing (Mercola and D'Adamo 2023). However, elaidic acid (C18:1n9-trans) showed an unexpected negative association with UPF intake (Menezes et al. 2023). These mixed findings, along with the weak Pearson correlation (<0.3), suggest that RBC membrane fatty acids may not reliably reflect UPF consumption in our adolescent population, possibly due to the complex and heterogeneous nature of UPFs.

A MD RBC membrane fatty acid signature was also created, which comprised four fatty acids: Gondoic Acid (C20:1n9), Arachidonic Acid (ARA, C20:4n6), Eicosapentaenoic Acid (EPA, C20:5n3), and Docosahexaenoic Acid (DHA, C22:6n3). This selection aligns well with the existing literature. Gondoic acid is present in small amounts in olive oil, a key component of the MD (Jimenez-Lopez et al. 2020), while arachidonic acid has been found to be inversely associated with MD adherence (Féart et al. 2011). Both EPA and DHA, long-chain

omega-3 fatty acids, are consistently associated with higher MD adherence (Ayats-Vidal et al. 2025; Féart et al. 2011; Girolì et al. 2021). Thus, this fatty acid signature agrees with previous findings. However, in this study, a strong Pearson correlation was not observed between this composite biomarker and MD adherence. Nonetheless, this signature still provided valuable insight into the relationship between MD patterns and neuropsychological outcomes in adolescents.

Limitations

This study has several strengths. First, its dual design, combining cross-sectional and longitudinal analyses in the context of a controlled trial, strengthens the ability to explore temporal relationships. The use of a validated dietary index (KIDMED) ensures reliable assessment of MD adherence, while the NOVA classification provides a standardised approach to UPF categorisation in epidemiological research. Extensive covariate adjustment and FDR correction further strengthen the robustness of the findings. The inclusion of polyphenol biomarkers, analysed in nearly half the sample, offers objective validation of UPF consumption and helps to mitigate measurement errors. Additionally, fatty acid biomarkers, also analysed in nearly half the sample, provide new insights into the relationship between MD adherence and neuropsychological outcomes.

Nevertheless, this study has some limitations. First, the FFQ used to assess dietary intake was not specifically validated for adolescents nor originally designed to classify foods according to processing level, which may have introduced misclassification of UPF consumption. Second, although UPF consumption did not significantly differ between baseline and the six-month follow-up, our analysis assumes that this stability reflects habitual intake; however, subtle or unmeasured dietary changes over time cannot be entirely excluded. Third, despite adjustment for baseline values of the outcome measures in the longitudinal models, which reduces the risk of reverse causation, residual confounding from unmeasured genetic or environmental factors cannot be ruled out. Fourth, there was a notable reduction in sample size at the second follow-up for all SDQ outcomes, which may have limited statistical power to detect potential longitudinal associations. This limitation was even more pronounced in the secondary analyses, where cross-sectional biomarker subsamples were halved, and longitudinal analyses experienced an even greater reduction, further decreasing statistical power. Fifth, self-reported data for both dietary and behavioural measures may be subject to reporting bias, and the latter also has limited reliability. However, the use of computerised cognitive tasks likely reduced subjective error in cognitive outcomes. Finally, the six-month follow-up period may be insufficient to capture longer-term neurodevelopmental effects, limiting our ability to draw conclusions about the sustained impact of dietary patterns on adolescent brain and behavioural development.

Future Research

These findings highlight the potential behavioural and cognitive benefits of the MD adherence compared to UPF consumption in adolescents. While our findings align with and extend existing evidence, most associations were cross-sectional, highlighting the need for future longitudinal studies with extended follow-up periods, larger and more diverse samples, and multiple neuropsychological assessments using adolescent-validated dietary assessment tools. Further investigation into underlying biological mechanisms is also warranted to better elucidate causal pathways. Given that adolescence is a critical period for shaping long-term dietary habits and neurodevelopment, there is an urgent need for targeted educational and policy interventions to promote adherence to healthful dietary patterns and reduce UPF consumption in youth, steps essential for safeguarding adolescent neuropsychological health.

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Appendix 1 - Approval Certificate for Master's Dissertation Development



ΕΛΛΗΝΙΚΟ ΜΕΣΟΓΕΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ
(ΕΛΜΕΠΑ)

Σχολή Επιστημών Υγείας
Τμήμα Κοινωνικής Εργασίας

Τ.Θ. 1939, Τ.Κ. 71004 Ηράκλειο
Πληροφορίες: Κων/νος Φραγκιαδάκης
Τηλέφωνο: 2810379534, Fax: 2810379504
Email: secretariat-socw@hmu.gr

Ηράκλειο: 11-09-2024
Αρ.Πρωτ.: 1988

ΒΕΒΑΙΩΣΗ

Με το παρόν βεβαιώνεται ότι, ο φοιτητής κ. **Μανίδης Αλέξιος** (ΜΥΧ47) είναι ενεργός φοιτητής του Δ.Π.Μ.Σ. «Διεπιστημονική Διαχείριση των Χρόνιων Νοσημάτων, της Αναπηρίας και της Γήρανσης» κι εκπονεί Διπλωματική Εργασία με τίτλο «Biomarkers of Dietary Patterns and Neuropsychological function in healthy Spanish adolescents», με επόπτη τον Επ. καθηγητή κ. Παπανδρέου Χριστόφορο, σύμφωνα με την με Αρ. πράξης 32/25.7.2024 απόφαση της Επιτροπής Προγράμματος Σπουδών του Δ.Π.Μ.Σ. ύστερα από αίτησή του (Αρ. Πρωτ. Αίτησης 1532/15-07-2024).

Η παραπάνω βεβαίωση χορηγείται στην ενδιαφερόμενη ύστερα από αίτημά της για να την χρησιμοποιήσει για κάθε χρήση.



Ο Προϊστάμενος Γραμματείας Τμήματος

Κων/νος Φραγκιαδάκης

Appendix 2 - Ethical Considerations

Participant Information Sheet

Qui som?

Jordi Julvez, investigador principal del projecte, treballa al Centre de Recerca en Epidemiologia Ambiental (CREAL, www.creal.cat) ubicat al Parc de Recerca Biomèdica de Barcelona (PRBB).

L'estudi el farà un equip de varies persones expertes en dieta i salut mental.

El projecte està finançat per l'*Instituto de Salud Carlos III del Ministerio de Economía y Competitividad*, del prestigiós Programa Miguel Servet.



Foto: Parc de Recerca Biomèdica de Barcelona (PRBB)

SMART-SNACK és un projecte que requereix de la participació voluntària d'escoles, pares i adolescents per aconseguir els seus objectius i arribar a conclusions útils per a tota la població.

Contacte:

Jordi Julvez (jjulvez@creal.cat)

Cecilia Persavento (mpersavento@creal.cat)

Número de telèfon: 93 214 73 88



Estudi SMART-SNACK

(Fruita de Temporada, Fruits Secs i Desenvolupament Mental del Adolescent: Una Intervenció en la Nutrició)

SMART-SNACK és un projecte de recerca

L'adolescència és un període fonamental per a la maduració del cervell i el desenvolupament mental, en el que intervenen múltiples factors. Diversos estudis realitzats han generat la hipòtesi que la dieta pot interferir en el desenvolupament mental. Descobrir quins aliments ens poden beneficiar i comprendre el seu paper en la salut dels adolescents és un dels reptes del nostre temps. Aquest coneixement permetrà crear recomanacions dietètiques més saludables i millorar la salut en un període tan important com és l'adolescència, on certs canvis poden marcar el futur per la resta de la vida.



Objectius

1.- Descobrir els efectes sobre el desenvolupament mental de dues intervencions de dieta, molt senzilles de seguir, durant 6 mesos, dirigides a adolescents. I en concret:

- Intervenció 1: menjar fruita de temporada

- Intervenció 2: menjar fruita de temporada + fruits secs.

2.- Avaluar les capacitats mentals dels adolescents abans i després de la intervenció dietètica a través de jocs informatitzats divertits i de fàcil aplicació.

3.- Avaluar si hi ha canvis en indicadors biològics de salut un cop finalitzada la intervenció dietètica.

Figure 6. Participant Information Sheet

Code CEIM-Ethics Approval



CONFIRMATION

I confirm that the “Parc de Salut MAR - Ethics Committee” has reviewed and approved

- ✓ The clinical study entitled: “Walnuts, Long-Chain Polyunsaturated Fatty Acids and Adolescent Brain Development: A Dietary Intervention”.

In which Dr. Jordi Júlvez Calvo is the principal investigator.

- ✓ and accompanied patient information sheet and informed consent form

under the reference number: 2015/6026/I

at the meeting of: January 27th, 2015



María Teresa Navarra Alcrudo
Secretary
Ethics Committee – Parc de Salut MAR

Barcelona, January 28th, 2015

CEIC – Parc de Salut MAR
Dr. Aiguader, 88 | 08003 Barcelona | Telèfon 93 316 06 77 | Fax 93 316 06 36
ceic-psmar@imim.es | www.parcdesalutmar.cat

Figure 7. Code CEIM-Ethics Approval

Informed Consent Form

Investigador: Jordi Julvez

Centre de Recerca en Epidemiologia Ambiental



Apreciado padre/madre/tutor,

El Centre de Recerca en Epidemiologia Ambiental (CREAL) es un centro de investigación que lleva a cabo estudios sobre el efecto de los factores medioambientales y de estilo de vida sobre la salud de las personas.

El CREAL ha ofrecido a varias escuelas/institutos la participación en un nuevo proyecto de investigación, el proyecto SMART-SNACK.

SMART-SNACK es un proyecto de investigación epidemiológica financiado por el Instituto de Salud Carlos III que necesita de **la participación voluntaria** de padres y adolescentes para poder llevar adelante sus objetivos y elaborar conclusiones a nivel poblacional.

SMART-SNACK tiene como objetivo investigar los efectos beneficiosos para el desarrollo mental durante la adolescencia de dos intervenciones dietéticas sencillas relacionadas con la ingesta regular de fruta de temporada y de frutos secos (nueces). Tales intervenciones sólo durarán seis meses. Para estudiar el efecto sobre el desarrollo mental, se administrará una serie de tests a los adolescentes participantes en dos ocasiones, al inicio de la intervención y al final de la misma. Estos tests se llevarán a cabo en la misma escuela/instituto.

La adolescencia es un periodo de grandes cambios y pensamos que es un buen momento para intervenir con una dieta más saludable y estudiar si tiene un efecto positivo en el desarrollo de las funciones intelectuales y de estado de ánimo.

Además, para poder ampliar el conocimiento sobre los efectos de la intervención dietética sobre la salud, es necesario conocer, por un lado, el papel de algunos genes en la predisposición a metabolizar mejor los nutrientes y por el otro lado saber si tales nutrientes han aumentado sus niveles en el organismo al finalizar la intervención. Si usted acepta participar en este estudio, un pequeño volumen de la muestra de sangre y saliva que se extraerá a su hijo/a se destinará al estudio de algunos genes y proteínas relacionadas con el metabolismo. Esta muestra se almacenará en el Centre de Recerca en Epidemiologia Ambiental (CREAL) hasta su análisis. Toda la información relacionada con el estudio genético será codificada para garantizar en todo momento la protección de sus datos personales.

Si ustedes lo autorizan, la participación de su hijo en el estudio implica que debe seguir las recomendaciones dietéticas y realización de algunos exámenes y procedimientos, que se detallan más adelante. La toma de las muestras biológicas será realizada por profesionales cualificados. Por otro lado, ustedes (los padres) deberán cumplimentar algunos cuestionarios sobre datos relacionados con el adolescente. Para la realización de este estudio **es totalmente necesaria su autorización** a través de los documentos adjuntos (hoja de consentimiento informado general y hoja de consentimiento informado genético), que deberán remitir **firmados** a la escuela en el **período de una semana** desde su recepción.

También encontrarán información más detallada del estudio.

Queremos pedirle la participación de su hijo/a junto con su colaboración y la de los colegios involucrados en el proyecto.

Estamos a su disposición por cualquier pregunta que quieran realizar, para ello pueden contactar con Cecilia Persavento (mpersavento@creal.cat), tel. 932147388).

Cordialmente,

Jordi Julvez Calvo

Investigador del Centre de Recerca en Epidemiologia Ambiental (CREAL)

Investigador principal del estudio SMART-SNACK



Procedimientos que se realizarán a todos los adolescentes del estudio

Preguntas habituales

LA INTERVENCIÓN DIETÉTICA Se pedirá el seguimiento de dos sencillas recomendaciones de dieta, una relacionada con el consumo regular de fruta de temporada y la otra incluye también la ingesta regular de frutos secos (30 g de nueces peladas al día, que serán proporcionadas de forma gratuita por nuestro centro). Habrá maneras divertidas para motivar a los adolescentes a seguir de forma correcta la intervención. Pediremos también a los padres que colaboren con el seguimiento. EXPLORACIÓN NEUROPSICOLÓGICA La exploración se realizará en las escuelas por los técnicos del estudio: Se realizarán dos evaluaciones (principio y final de la intervención) de 40 minutos de duración del desarrollo intelectual mediante los tests NBack (memoria) y ANT (atención), Tapping Test (velocidad motora), Raven test (cociente de inteligencia), TMT (Atención y velocidad motora), Test de la ruleta (decisión-riesgo), Test de reconocimiento de expresiones faciales (empatía). El adolescente también responderá a un breve cuestionario de comportamiento (SDQ) que dura unos 5 minutos. TOMA DE MUESTRAS BIOLÓGICAS En cada una de las dos visitas se recogerán muestras de sangre y saliva (solo la 1ª visita) para el estudio de los nutrientes que puedan influir en el desarrollo y crecimiento de los adolescentes. La recogida de muestras no supone ningún riesgo y se hará en un centro sanitario. Se extraerá una pequeña cantidad de sangre (10 mililitros) para medir los niveles varias proteínas y ácidos grasos relacionados con el consumo de frutos (frescos y secos). Aquellos participantes que desestimen dar sangre podrán seguir en el proyecto. Se extraerá saliva para medir determinadas variantes genéticas relacionadas con el metabolismo de nutrientes y el desarrollo mental. El análisis sirve para poder ampliar el conocimiento sobre los efectos de esta intervención sobre la salud, es necesario conocer el papel de algunos genes en la predisposición a absorber de manera eficiente los ácidos grasos. Este análisis marcadores genéticos se realizará en el Centre de Regulació Genètica (CRG). El ADN restante se almacenará de forma segura en el CREAL para futuros estudios relacionados con determinantes ambientales y neurodesarrollo, hasta que la muestra de agote. CUESTIONARIOS Y ENCUESTAS Los padres responderán un cuestionario de salud general (30 minutos) y un cuestionario sobre la dieta de su hijo (20 minutos), éste último tres veces. Los Tutores de las escuelas/institutos responderán un breve cuestionario de comportamiento del adolescente (5 minutos). Los adolescentes también responderán un cuestionario general (10 minutos). OBJETIVOS SECUNDARIOS Medición de peso, talla, presión arterial y prueba de capacidad pulmonar (espirometría): Se realizarán dos evaluaciones de peso talla y presión arterial. La exploración se realizará en las escuelas por los técnicos del estudio. Factores ambientales: Se harán también estudios de cómo factores ambientales influyen en las capacidades mentales, por ejemplo, estimar la contaminación atmosférica de los sitios por donde pasa su hijo/a a través de una aplicación al móvil.	¿POR CUÁNTO TIEMPO PERMANECERÉ EN EL ESTUDIO? Para obtener resultados en este tipo de estudios se requiere el seguimiento de los participantes durante 6 meses. Ustedes pueden retirar su consentimiento en cualquier momento. Sin embargo, si decidieran retirarse del estudio, les aconsejamos que hable primero con los investigadores. En relación a las muestras biológicas, todo el material que no sea utilizado inmediatamente será conservado durante un máximo de 50 años para realizar, posiblemente, posteriores determinaciones. Sus muestras, hasta su uso en el proyecto de investigación, formarán parte del bio-depósito del estudio. Su cesión anonimizada a investigadores de otros centros estará mediada a la aprobación del Comité Científico del estudio. También cabe la posibilidad de ser re-contactado en el futuro. ¿CUÁNTAS VISITAS SE VAN A REALIZAR EN ESTOS 6 MESES? Habrà dos visitas. Una al principio, antes de iniciar la intervención dietética. Y otra al final, tras los 6 meses, al finalizar la intervención. ¿RECIBIRÉ ALGÚN BENEFICIO POR PARTICIPAR EN EL ESTUDIO? Es probable que a corto plazo obtenga beneficios para la dieta y la salud. También esperamos que la información que se obtenga como resultado de este estudio beneficie en el futuro la calidad de vida de las actuales y futuras generaciones de adolescentes. Para los participantes que accedan a dar muestras de sangre recibirán los resultados de un chequeo rutinario. ¿SE MANTENDRÁ CONFIDENCIAL? Los datos estarán protegidos de acuerdo a la Ley 15/99 de Protección de Datos Personales*. El uso que se haga de la información obtenida será confidencial. Por lo tanto, la identidad del adolescente será siempre preservada. Igualmente los datos obtenidos sólo podrán ser publicados de forma anónima, de forma agregada y no individual. ¿CUÁLES SON LOS RIESGOS? Si al ingerir estos frutos secos aparecen, erupciones o edemas por el cuerpo, o tal vez mareos, vómitos o hinchazón en la boca (lengua, garganta) o una importante dificultad al respirar, hay que llamar al número 112 o acudir a urgencias médicas. Tal vez sea esta la primera crisis alérgica frente a las nueces y esos signos y síntomas un primer aviso agudo que requiera atención inmediata. Se ha contratado una póliza de responsabilidad civil y en caso de sufrir cualquier problema de salud derivado de la participación en el estudio, podrá reclamar compensación económica. Para tramitación de la misma llamar a la correduría de seguros OPTIM INSURANCE BROKER tel. 934589110 / 914492646. ¿CUÁLES SON LOS COSTES? Su participación en este estudio no representará ningún coste para ustedes. Ustedes no recibirán ninguna remuneración por participar en el estudio. Aunque pequeños obsequios formarán parte de la intervención con el fin de estimular la motivación. ¿CUÁLES SON LOS DERECHOS COMO PARTICIPANTE? La participación en el estudio es voluntaria. Ustedes pueden escoger no participar o pueden abandonar el estudio en cualquier momento. El retirarse del estudio no representará ninguna penalidad o pérdida de beneficios a los que su hijo tiene derecho. ¿A QUIÉN DEBO LLAMAR SI TENGO UNA PREGUNTA O UN PROBLEMA?
*En cumplimiento de lo establecido por el artículo 5 de la Ley Orgánica 15/1999, de 13 de diciembre, ponemos en su conocimiento que sus datos personales serán incorporados a un fichero titularidad de la Fundación CREAL con domicilio en calle Doctor Aiguader, 88, 08003, Barcelona. La finalidad del tratamiento es desarrollar una investigación epidemiológica avanzada sobre factores ambientales que afectan a la salud humana, para mejorar las recomendaciones en salud pública. En cualquier caso, usted podrá ejercitar los derechos de oposición, acceso, rectificación y cancelación, mediante escrito dirigido a la dirección anteriormente señalada, acompañando copia de su D.N.I. o documento equivalente que acredite su identidad.	

Para preguntar acerca del estudio o por aspectos relacionados con la investigación puede contactar con Cecilia Persavento en el número de teléfono 932147388.

¿DÓNDE PUEDO OBTENER MÁS INFORMACIÓN?

Podrán encontrar información sobre SMART-SNACK en:

<http://www.creal.cat/programes-recerca/projectes-creal/136/estudi-smart-snack?prog=2>



Hoja de Consentimiento Informado

(Copia Padres)

Yo,..... (Nombre, apellidos y teléfono de contacto), en calidad de..... (Relación con el participante).

Yo,..... (Nombre, apellidos y teléfono de contacto), en calidad de..... (Relación con el participante) del adolescente..... (Nombre, apellidos y fecha de nacimiento).

- Hemos leído la hoja de información que se nos ha entregado.
- Hemos podido hacer preguntas sobre el estudio.
- Hemos recibido suficiente información sobre el estudio.
- Hemos hablado con....., quien nos ha aclarado las dudas.
- Comprendemos que nuestra participación es voluntaria.
- Comprendemos que podemos retirarnos del estudio:
 - Cuando queramos
 - Sin tener que dar explicaciones
 - Sin que esto repercuta en los cuidados médicos del adolescente
- Comprendemos que el estudio está diseñado para incrementar los conocimientos médicos.
- Comprendemos que todos los resultados son confidenciales y que sólo nosotros, si los pedimos, y los responsables del estudio los conoceremos.
- Prestamos libremente nuestra conformidad para participar en el estudio.
- Prestamos libremente nuestra conformidad para contactar con nosotros para preguntarnos si queremos participar en futuros estudios parecidos a éste desde el CREAL.
- Nombre del centro educativo y curso:.....
- ¿Es su hijo/a alérgico alguna fruta fresca o frutos secos? No.... / Sí, indica cuáles:.....
- ¿Hay algunos frutos secos (ej. nueces, etc.) que no les gusten a su hijo/a? No.... / Sí, indica cuáles:.....
- ¿Sufre su hijo/a alguna enfermedad física o neurológica? No.... / Sí, indicaCuál:
- ¿Ha estado su hijo/a participando en el proyecto BREATHE? No.... / Sí.... ¿O algún otro estudio sobre salud mental o nutrición durante los últimos 3 meses? No.... / Sí....
- Si hay hermanos/as que también participarán en el estudio SMART SNACK, por favor indique, nombre, apellidos, centro y curso:.....

Firma del padre / de la madre o tutor legal

DNI:

Fecha y lugar:, a..... De..... De 20....

Firma del/la menor participante

DNI:

Firma del responsable del estudio

Nombre y apellidos.....Jordi Julvez Calvo.....

Usted recibirá una copia de este formulario. Puede también pedir una copia del protocolo (plan completo del estudio) directamente telefoneando a Cecilia Persavento (93 214 73 88).

Hoja de Consentimiento Informado Genético

(Copia Padres)

Toda la información relacionada con el estudio genético se almacenará en la más estricta confidencialidad, como se requiere por la Ley 15/99 de Protección de Datos Personales y la Ley 14/2007 de Investigación Biomédica. Toda la información será codificada y tratada de forma anónima; dispondremos de un número de estudio para vincular toda la información relacionada con usted. Sólo algunos miembros del equipo del proyecto podrán tener acceso la información obtenida. **¿Qué posibles ventajas nos puede proporcionar, participar en el proyecto?** El estudio no tiene como objetivo identificar las variantes genéticas con una alta predisposición a la enfermedad. No puede haber ningún hallazgo que tenga implicaciones para la salud de su hijo. **¿Qué posibles desventajas nos puede proporcionar, participar en el proyecto?** Si usted decide que su hijo participe en este estudio, se le recogerá una pequeña cantidad de sangre. La cantidad de sangre que se recoge no supone ningún efecto adverso para su salud, sin embargo, pueden aparecer algunas complicaciones menores derivadas de la punción, como mareos o pequeños hematomas.



Appendix 3 - Research tools (extended)

Neuropsychological and behavioural testing for primary endpoints

Attention

Assessed with the Attention Network Test (ANT) (2), a computerized test examining sustained attention based on reaction times (RT) to target stimuli. The test consisted of the appearance of five arrows on the screen, and participants had to indicate the direction of the central arrow as fast as possible. The ANT measures three distinct cognitive attention domains: alerting, orienting, and executive control. The alerting component measures the ability to achieve and sustain vigilance by comparing reaction times between no cue and double cue conditions. The orienting component measures the ability to shift attention to a specific spatial location by comparing reaction times between centre cue and spatial cue conditions. The executive control component measures conflict resolution by comparing reaction times between incongruent and congruent flanker conditions. For all components, the outcome is measured in milliseconds, and lower scores indicate better attention performance.

Working Memory

Measured with the N-back task (3), a computer-based test assessing working memory (WM) using series of numbers. The outcome selected for this test was d prime (d'): $d' = z(\text{hit rate}) - z(\text{false alarm rate})$. A higher d' indicates better detection and, thus, a more accurate performance. In this test, a sequence of items is shown, and for each item it must be determined whether the last one shown is identical to the stimulus presented “n” trials back (1-, 2-, 3- and 4-back). These different conditions are known as loads, and in the highest cognitive load (i.e., 4-back) the demands on WM are stronger. For this study, the 4-back test was used.

In the 4-back level, the target was any stimulus identical to the one presented four trials previously. The more correct answers, the higher the score.

Fluid Intelligence

Evaluated using an inductive reasoning subtest (i.e., fluid intelligence) of the Tests of Primary Mental Abilities (PMA-R, the Spanish adaptation) (4). The test consists of choosing a letter from a set of six possible alternatives, underlying a given sequence of letters. The total score is the number of correct item responses. The more correct answers, the higher the score.

Advantageous Decision-Making

Assessed with the Roulettes Task (5), a gambling task adapted from the Cups Task which assesses risky decision-making, specifically whether participants adjust their risky behaviours according to the probabilities and importance of the outcome (cognition influenced by emotion). The Roulettes Task is a game of chance with the goal of making as much money as possible. Two roulettes appear on the screen; each divided into segments with varying amounts of money. The left roulette has one segment with a larger amount, for example \$2, while the other segments are empty (\$0), making it the risky option since the chance of winning depends on the number of segments. The right roulette is the safe option, with all segments containing the same amount, \$1, guaranteeing a win of \$1 on each spin. Additionally, roulettes can be red or blue, indicating money loss and gain, respectively. In this study, we focused specifically on the advantageous decision-making (gain) condition as it reflects reward-seeking behaviour and positive risk-taking, which are particularly relevant during adolescence when reward sensitivity is heightened due to ongoing neurodevelopmental changes in the dopaminergic system (6). The gain condition better captures the decision-making processes most pertinent to this developmental stage. The scores are measured as total risk adjustment to assess risk sensitivity, with values closer to 0 indicating greater risk insensitivity.

Behavioural Problems

A self-reported version of the Strengths and Difficulties Questionnaire (SDQ, Spanish adaptation) (7) was used, which gave a total score of problem behaviour. It consists of 25 questions, organized in a general score of problem behaviour and five sub-scales aimed to assess emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and pro-social behaviour. For our analyses, the SDQ was grouped to derive internalising (emotional symptoms and peer relationship problems; 10 items) and externalising (conduct problems and hyperactivity/inattention; 10 items) scores, as previously described (8). A higher score indicates a more problematic behaviour.

Attention-Deficit/Hyperactivity Disorder

The attention deficit/hyperactivity disorder (ADHD) DSM-IV form list (9) was completed by the teacher, who answered 18 multiple-choice questions to rate the ADHD performance in a general score of the participant (adolescent). The scores were transformed into the number of symptoms and diagnostic criteria for ADHD. Based on DSM-IV criteria, a binary variable indicating ADHD symptom diagnosis (no/yes) was derived at both baseline and follow-up

assessments, with a threshold of 6 or more symptoms in either the inattentive or hyperactive-impulsive domains indicating a positive ADHD symptom diagnosis.

Covariate details

The following variables were included as covariates in the final models: age (continuous, years), sex (male, female), BMI z-score (continuous), maternal ethnicity (Spanish, other), substance use (yes: any use of cigarette, e-cigarette, alcohol, cannabis, or other drugs; no), maternal educational attainment (high school studies or lower, university studies, according to ISCED criteria), physical activity (up to once a week, twice a week, three times a week, more than three times a week), and annual net household income (low: €21,000–€34,000; moderate: €34,000–€41,000; high: €41,000–€84,000). Diagnosed maternal mental disorder (no, yes) was included as a covariate depending on the specific exposure. These covariates were collected using study-specific questions. For longitudinal analyses, models were further adjusted for randomisation group (control, intervention) and baseline outcome measurement.

References

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- 2) Forns J, Esnaola M, López-Vicente M, et al. The n-back test and the attentional network task as measures of child neuropsychological development in epidemiological studies. *Neuropsychology* 2014; 28: 519–29.
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- 5) Levin IP, Weller JA, Pederson AA, Harshman LA. Age-related differences in adaptive decision making: Sensitivity to expected value in risky choice. *Judgm Decis Mak* 2007; 2: 225–33.
- 6) Galván, A. (2013). The Teenage Brain: Sensitivity to Rewards. *Current Directions in Psychological Science*, 22(2), 88-93. <https://doi.org/10.1177/0963721413480859>.
- 7) Ortuño-Sierra J, Fonseca-Pedrero E, Paino M, Sastre I Riba S, Muñiz J. Screening mental health problems during adolescence: psychometric properties of the Spanish version of the Strengths and Difficulties Questionnaire. *J Adolesc* 2015; 38: 49–56.
- 8) Goodman A, Lamping DL, Ploubidis GB (2010) When to use broader internalising and externalising subscales instead of the hypothesised five subscales on the Strengths and Difficulties Questionnaire (SDQ): data from British parents, teachers and children. *Journal of Abnormal Child Psychology*, 38, 1179-1191.
- 9) American Psychiatric Association. 2000. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR®* (4th ed, text revision). Washington, DC American Psychiatric Association.

Secondary endpoints

- 1) Height, weight, and waist circumference were measured by standard methods. Height was measured using the stadiometer model SECA 214, weight by the weighting scale SECA 770 model, and waist circumference with the SECA 201 tape model. Body mass index was calculated based on weight/height². All measurements were collected by a trained nurse at the schools at baseline and after 6 months of intervention.
- 2) For the determination of omega 3 fatty acids, a nurse obtained blood samples after an overnight fast. The samples were centrifuged at 2500g for 20 minutes at 20°C within 4 hours after extraction. We obtained a 1500-μL aliquot of packed RBCs, which was stored at -80°C until fatty acid analysis. We determined the fatty acid profile in RBC by gas-chromatography, as described. (8) In brief, cells contained in a 100-μL aliquot of RBCs were haemolysed and spun. The pellet membranes were dissolved in 1 mL BF₃ methanol solution and heated to hydrolyse and methylate glycerophospholipid fatty acids contained in the RBC membrane. The fatty acid methyl esters were isolated by adding n-hexane and were separated by gas chromatography using an Agilent HP 7890 Gas Chromatograph equipped with a 30 m × 0.25 μm × 0.25 mm SupraWAX-280 capillary column (Teknokroma, Barcelona, Spain), an autosampler, and a flame ionization detector. The amount of each fatty acid was expressed as a percentage of the total identified fatty acids in the sample.
- 3) Urine samples (5 μL) were diluted 1:20 (v/v) with Milli-Q water containing 0.05% formic acid, with abscisic acid-D6 used as the internal standard at a final concentration of 100 ppb. Chromatographic separation was performed on a Kinetex F5 100 Å (50 × 4.6 mm, 2.6 μm) column (Phenomenex), equipped with a SecurityGuard™ UHPLC F5 4.6 mm pre-column, and maintained at 40°C. The mobile phases were 0.05% acetic acid in water (A) and 0.05% acetic acid in acetonitrile (B), using a non-linear gradient at a flow rate of 0.75 mL/min. Metabolites were quantified using calibration curves prepared in synthetic urine; where standards were unavailable, the corresponding aglycone calibration curves were used. Identification and quantification were performed with Agilent MassHunter Software.

Appendix 4 - Supplementary Material

Fatty Acid	Spearman Correlation	P-value
Docosahexaenoic Acid (DHA) (C22:6n3)	-0.110	0.054
Elaidic Acid (C18:1 trans-9)	-0.105	0.066
Eicosapentaenoic Acid (EPA) (C20:5n3)	-0.092	0.110
Linoleic Acid (LA) (C18:2n6)	0.086	0.136
Eicosadienoic Acid (C20:2n6)	0.085	0.139
Docosapentaenoic Acid (DPA) (C22:5n3)	-0.078	0.175
Arachidic Acid (AA) (C20:0)	-0.076	0.186
Osbond Acid (C22:5n6)	0.062	0.281
Adrenic Acid (C22:4n6)	0.058	0.309
Myristic Acid (C14:0)	-0.052	0.364
Dihomo- γ -Linolenic Acid (GLA)(C20:3n6)	0.050	0.382
Arachidonic Acid (ARA) (C20:4n6)	0.045	0.435
Oleic Acid (C18:1n9, cis)	-0.045	0.437
Stearic Acid (C18:0)	0.039	0.496
Alpha-Linolenic Acid (ALA) (C18:3n3)	-0.028	0.621
Nervonic Acid (C24:1n9)	-0.027	0.644
Behenic Acid (C22:0)	-0.021	0.716
Palmitoleic Acid (C16:1 trans-7)	-0.010	0.862
Palmitoleic Acid (C16:1n7)	0.009	0.873
Calendic Acid (C18:3n6)	0.007	0.909
Gondoic Acid (C20:1n9)	-0.006	0.915
Lignoceric Acid (C24:0)	<0.001	0.998
Palmitic Acid (C16:0)	<0.001	0.999

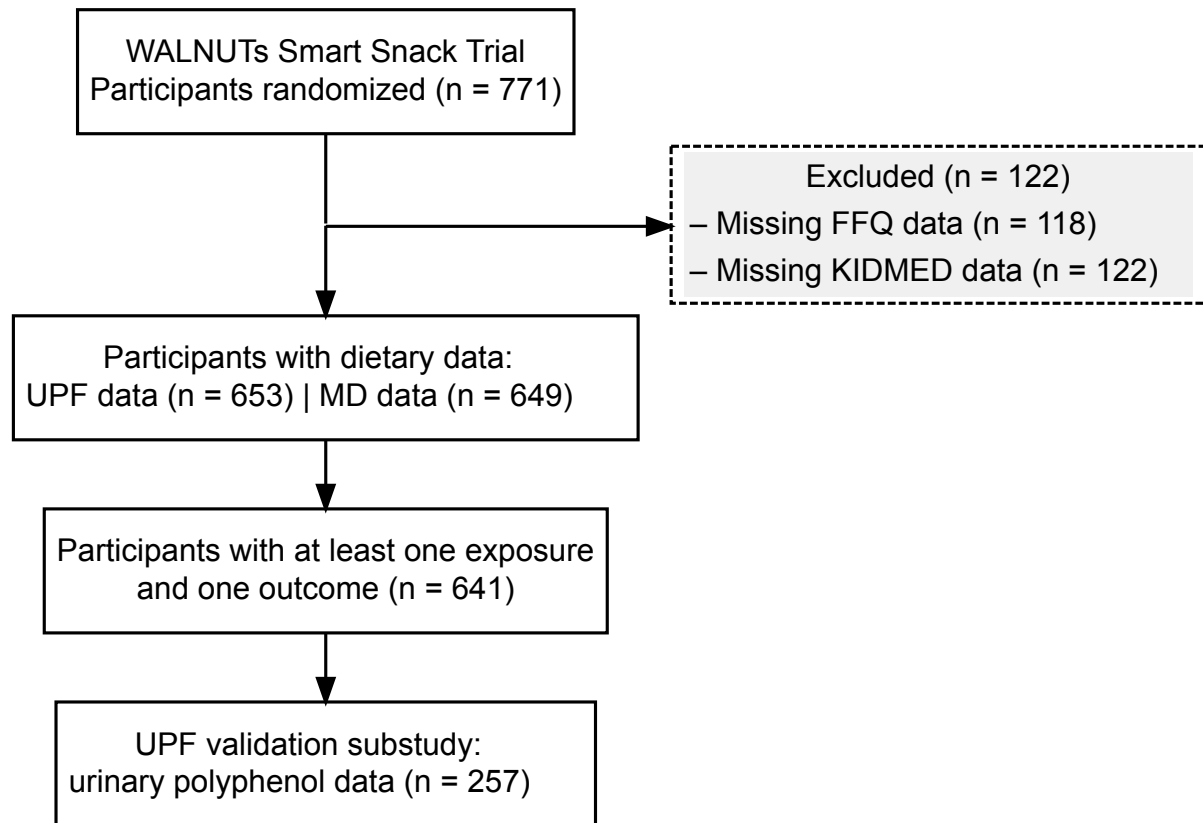
Supplementary Table 1 Bivariate correlations between %UPF consumption (in grams/d) and RBC membrane fatty acids. These exploratory analyses were not used in the main statistical models and are presented here for transparency.

Polyphenol	Spearman Correlation	P-value
Sinapic acid sulfate	-0.184	0.003
Enterodiol glucuronide	-0.156	0.012
Ferulic acid glucuronide	-0.153	0.014
Ferulic acid sulfate	-0.149	0.016
Syringic acid sulfate	-0.140	0.024
Enterolactone glucuronide	-0.127	0.040
Syringic acid	-0.116	0.062
Coumaric acid glucuronide	-0.115	0.065
Catechol sulfate	-0.114	0.067
Homovanillic acid glucuronide	0.067	0.278
Hydroxytyrosol sulfate	0.059	0.340
Protocatechuic acid glucuronide	0.058	0.351
4-hydroxybenzoic acid	-0.047	0.454
Protocatechuic acid sulfate	-0.031	0.621
Hydroxytyrosol sulfate	-0.027	0.660
Vanillic acid glucuronide	0.008	0.902
Dihydrocaffeic acid glucuronide	0.007	0.907
Dihydrocaffeic/Homovanillic sulfate	-0.002	0.980
Homovanillic acid	0.001	0.991

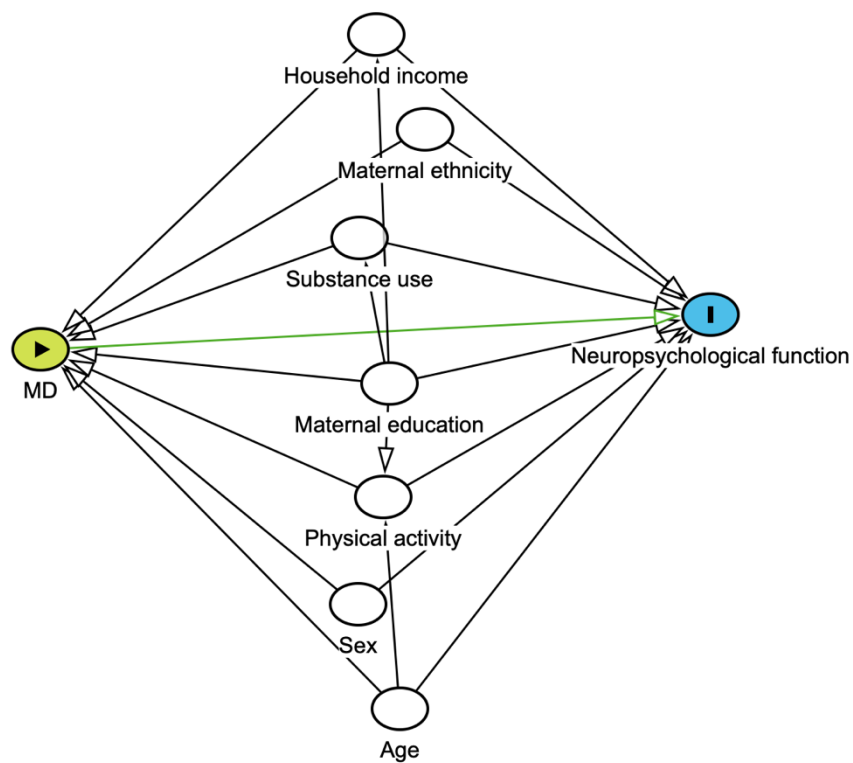
Supplementary Table 2 Bivariate correlations between %UPF consumption (in grams/d) and urinary polyphenols. These exploratory analyses were not included in the main statistical models and are presented here for transparency.

Fatty Acid	Spearman Correlation	P-value
Arachidonic Acid (ARA) (C20:4n6)	-0.191	0.001
Eicosapentaenoic Acid (EPA) (C20:5n3)	0.162	0.004
Adrenic Acid (C22:4n6)	-0.132	0.021
Eicosadienoic Acid (C20:2n6)	-0.113	0.049
Oleic Acid (C18:1n9, cis)	0.109	0.057
Docosahexaenoic Acid (DHA) (C22:6n3)	0.104	0.070
Stearic Acid (C18:0)	-0.102	0.076
Palmitic Acid (C16:0)	0.087	0.130
Osbond Acid (C22:5n6)	-0.086	0.136
Alpha-Linolenic Acid (ALA) (C18:3n3)	0.067	0.242
Palmitoleic Acid (C16:1 trans-7)	0.057	0.320
Palmitoleic Acid (C16:1n7)	0.054	0.351
Arachidic Acid (AA) (C20:0)	0.048	0.406
Docosapentaenoic Acid (DPA) (C22:5n3)	-0.043	0.458
Myristic Acid (C14:0)	0.037	0.519
Lignoceric Acid (C24:0)	-0.035	0.543
Nervonic Acid (C24:1n9)	0.031	0.584
Gondoic Acid (C20:1n9)	0.030	0.604
Calendic Acid (C18:3n6)	0.029	0.616
Linoleic Acid (LA) (C18:2n6)	-0.026	0.652
Elaidic Acid (C18:1 trans-9)	0.014	0.804
Behenic Acid (C22:0)	0.003	0.953
Dihomo-Gamma-Linolenic Acid (GLA)(C20:3n6)	0.003	0.964

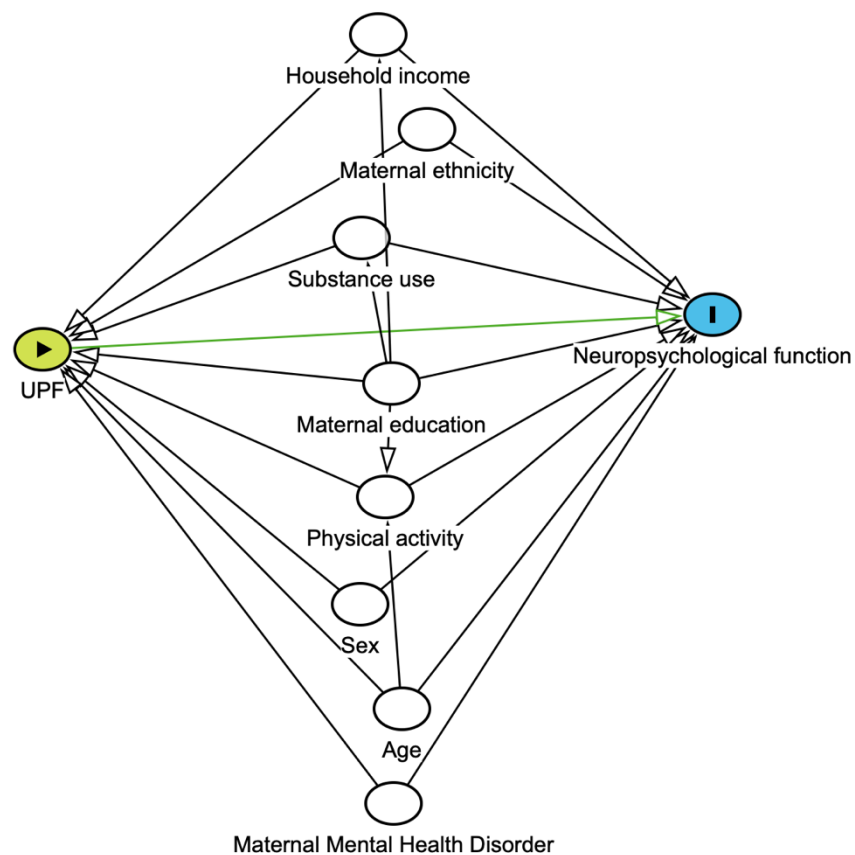
Supplementary Table 3 Bivariate correlations between MD adherence and RBC membrane fatty acids. These exploratory analyses were not used in the main statistical models and are presented here for transparency.



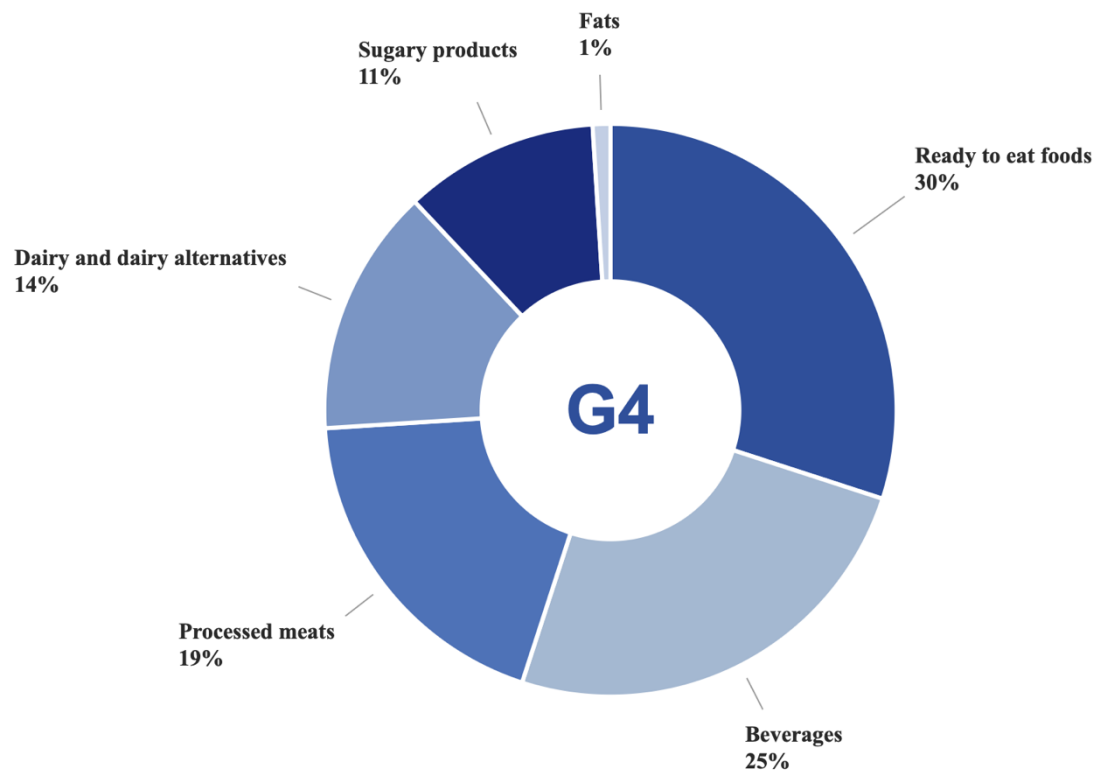
Supplementary Figure 1. Flow chart showing participant selection from initial randomization (n=771) through exclusions for missing FFQ and KIDMED data (n=122), to final analytical samples for dietary data analysis (n=641) and UPF validation substudy (n=257). UPF = Ultra-Processed Food; MD = Mediterranean Diet; FFQ = Food Frequency Questionnaire.



Supplementary Figure 2. Directed Acyclic Graph illustrating the causal relationships between Mediterranean diet (MD) and neuropsychological function. The minimal sufficient adjustment set includes age, household income, maternal education, maternal ethnicity, physical activity, sex and substance use. All white nodes represent the covariates required to estimate the unbiased total causal effect of MD on neuropsychological outcomes.



Supplementary Figure 3. Directed Acyclic Graph illustrating the causal relationships between Ultra-processed Food (UPF) intake and neuropsychological function. The minimal sufficient adjustment set includes age, household income, maternal education, maternal ethnicity, physical activity, sex, substance use, and maternal mental health disorder. All white nodes represent the covariates required to estimate the unbiased total causal effect of UPF on neuropsychological outcomes.



Supplementary Figure 1. Relative contribution of each food group to ultra-processed food and drinks consumption in MB scenario at baseline (NOVA classification, group 4) in participants of the WALNUTs Smart Snack Trial. This figure is provided for informational purposes only, to illustrate the relative contribution of each food group to overall UPF intake in the study population.

Section 1: Application of NOVA Processing Classification to FFQ1 and FFQ2 Food Items Under Three Dietary Scenarios

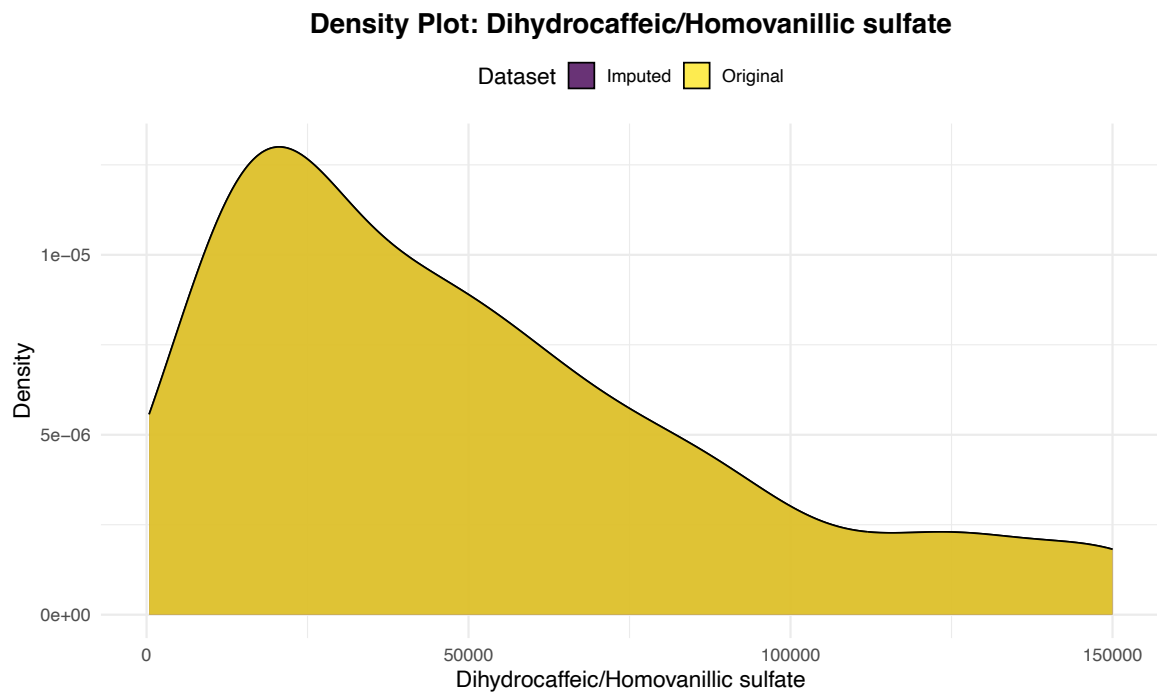
<i>Item</i>	<i>Food Item</i>	<i>NOVA-LB</i>	<i>NOVA-MB</i>	<i>NOVA-UB</i>
<i>gd_whole_milk_1</i>	Milk and plain yoghurt	1	1	4
<i>gd_skimmed_milk_1</i>	Milk and plain yoghurt	1	1	4
<i>gd_milk_omega3_1</i>	Dairy desserts and drinks (Ultra Processed versions)	4	4	4
<i>gd_vegetable_drink_1</i>	Dairy substitute products	4	4	4
<i>gd_yogurt_1</i>	Milk and plain yoghurt	1	1	4
<i>gd_skimmed_yogurt_1</i>	Milk and plain yoghurt	1	1	4
<i>gd_petitsuisse_1</i>	Dairy desserts and drinks (Ultra Processed versions)	3	4	4
<i>gd_soya_yogurt_1</i>	Yoghurt substitute	4	4	4
<i>gd_hard_cheese_1</i>	Cheese	3	3	4
<i>gd_lowfat_cheese_1</i>	Cheese	3	3	4
<i>gd_omelette_fried_eggs_1</i>	Omelette	1	3	3
<i>gd_eggs_omega3_1</i>	Egg	1	1	1
<i>gd_chicken_1</i>	Chicken	3	3	4
<i>gd_beef_pork_1</i>	Beef	3	3	4
<i>gd_frankfurt_1</i>	Sausages	4	4	4
<i>gd_cold_meat_1</i>	Processed meat	3	4	4
<i>gd_ham_1</i>	Salted, smoked or canned meat, without additives	3	3	4
<i>gd_whitefish_1</i>	Fish	1	1	4
<i>gd_fattyfish_big_1</i>	Fish	1	3	4
<i>gd_fattyfish_small_1</i>	Fish	1	3	4
<i>gd_canned_fish_1</i>	Salted, smoked or canned fish	3	3	4
<i>gd_molluscs_1</i>	Sea food	1	1	4
<i>gd_fish_derivatives_1</i>	Processed meat (beef, pork and fish)	4	4	4
<i>gd_raw_vegetables_1</i>	Vegetables	1	1	4
<i>gd_cooked_vegetables_1</i>	Vegetables	1	3	4
<i>gd_tomato_sauce_1</i>	Vegetables	1	3	4
<i>gd_legumes_1</i>	Beans, lentils and chickpeas	1	1	4
<i>gd_orange_1</i>	Fruit	1	1	4
<i>gd_apple_1</i>	Fruit	1	1	4
<i>gd_watermelon_1</i>	Fruit	1	1	4
<i>gd_strawberries_1</i>	Fruit	1	1	4
<i>gd_peach_1</i>	Fruit	1	1	4
<i>gd_otherfruits_1</i>	Fruit	1	1	4

<i>gd_walnuts_1</i>	Nuts and Seeds	1	1	4
<i>gd_hazelnuts_1</i>	Nuts and Seeds	1	1	4
<i>gd_almonds_1</i>	Nuts and Seeds	1	1	4
<i>gd_other_nuts_1</i>	Nuts and Seeds	1	1	4
<i>gd_seeds_1</i>	Nuts and Seeds	1	1	4
<i>gd_white_bread_1</i>	Bread	3	3	4
<i>gd_integral_bread_1</i>	Bread	3	3	4
<i>gd_cereals_breakfast_1</i>	Breakfast cereals	3	4	4
<i>gd_integral_cereal_breakfast_1</i>	Breakfast cereals	3	4	4
<i>gd_pizza_1</i>	Pizza and focaccia (dough)	3	4	4
<i>gd_homemade_fries_1</i>	Potato products	3	3	3
<i>gd_industrial_fries_1</i>	Potato products	4	4	4
<i>gd_rice_pasta_1</i>	Rice, Pasta, Corn	1	1	4
<i>gd_biscuits_pastries_1</i>	Biscuits	4	4	4
<i>gd_chocolate_pastries_1</i>	Pastries, buns, and cakes	4	4	4
<i>gd_chocolates_1</i>	Dairy desserts and drinks	3	4	4
<i>gd_chocolate_powder_1</i>	Sauces, dressing and gravies - also in powder/dehydrated form/condensed form	1	4	4
<i>gd_sugar_honey_candy_1</i>	Sweet snacks	2	4	4
<i>gd_olive_oil_1</i>	Plant oil	2	2	4
<i>gd_other_oil_1</i>	Plant oil	2	2	4
<i>gd_butter_1</i>	Animal fats	2	2	3
<i>gd_butter_omega3_1</i>	Animal fats	4	4	4
<i>gd_mayonnaise_1</i>	Animal fats	3	4	4
<i>gd_soft_drinks_1</i>	Soft drinks	4	4	4
<i>gd_soft_drinks_light_1</i>	Soft drinks	4	4	4
<i>gd_natural_fruit_juice_1</i>	Fruit juice fresh and smoothies	1	1	4
<i>gd_packaged_fruit_juice_1</i>	Fruit drinks, iced tea and other sweetened beverages	3	3	4

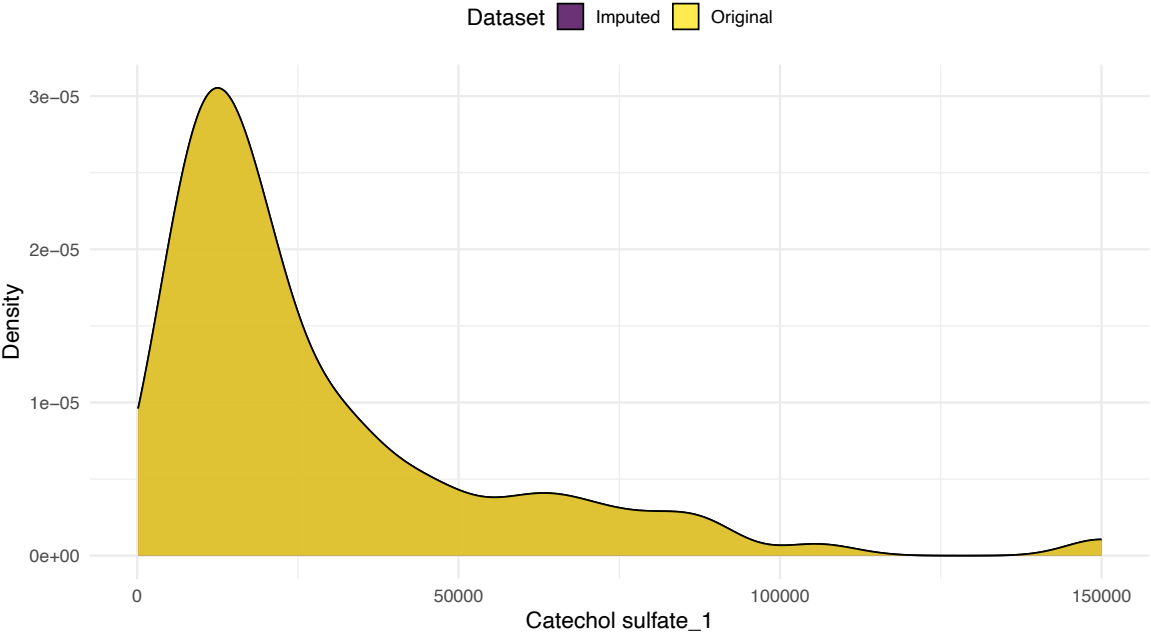
Supplementary Table 4 Categorisation of FFQ1 and FFQ2 food items according to the NOVA processing classification under three processing scenarios.

Section 2: Imputation and Quality Control of Urinary Polyphenols

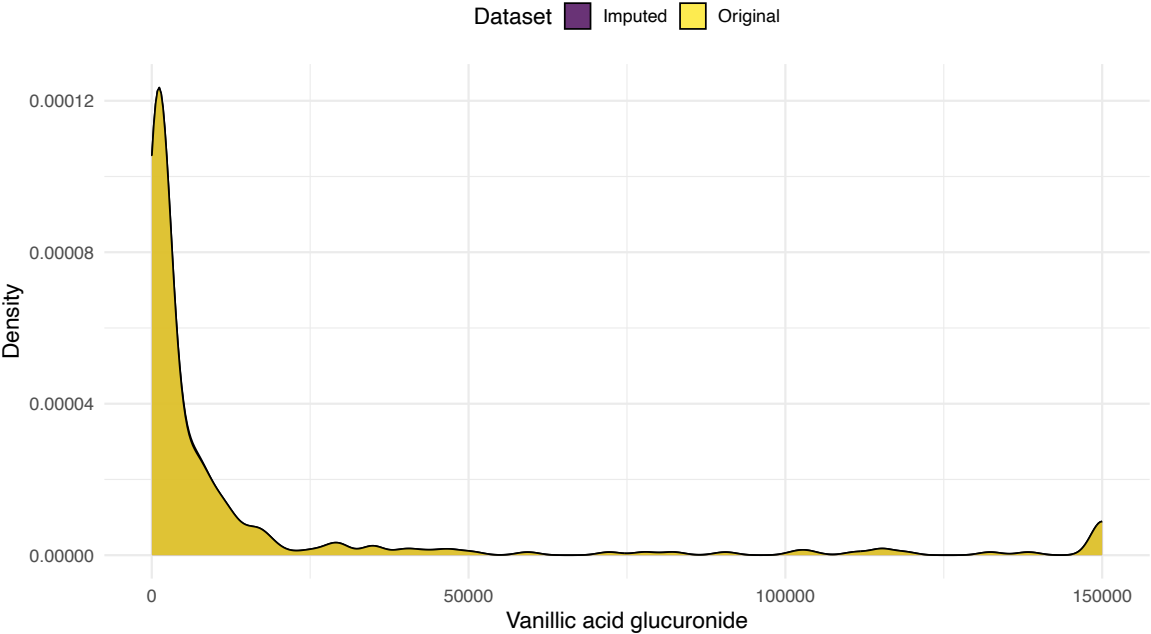
Imputation was conducted for all polyphenols with less than 20% missing values. Quality control was evaluated by visual inspection of density plots, which compare the distributions of the original and imputed data for each metabolite.

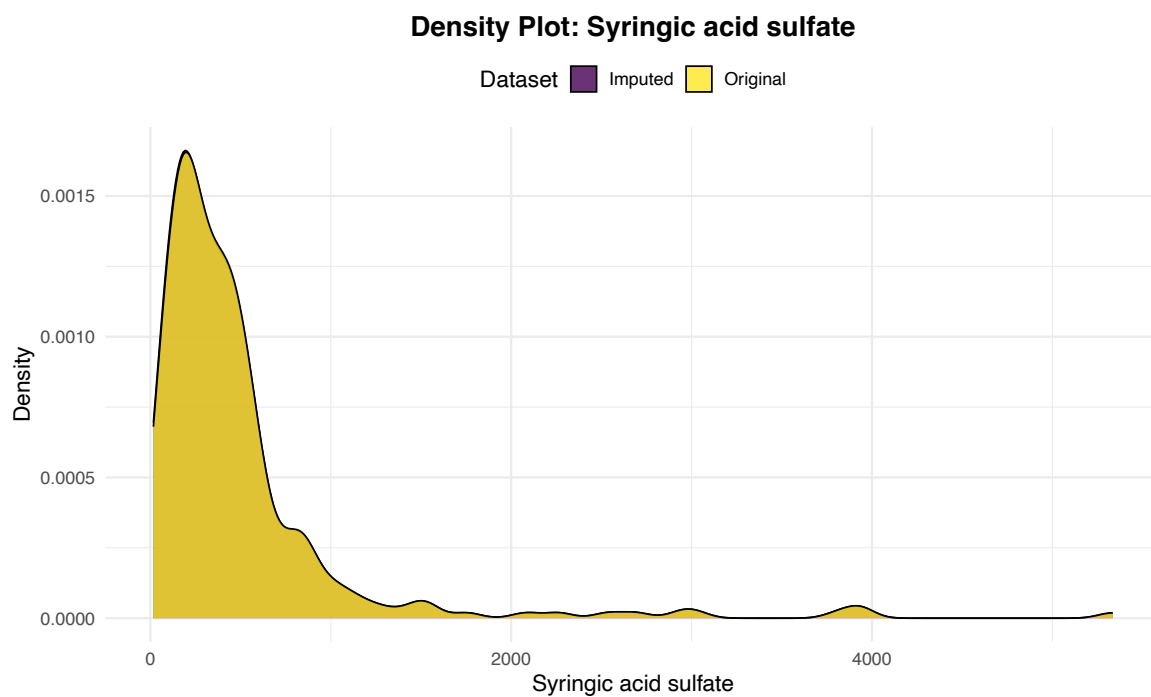
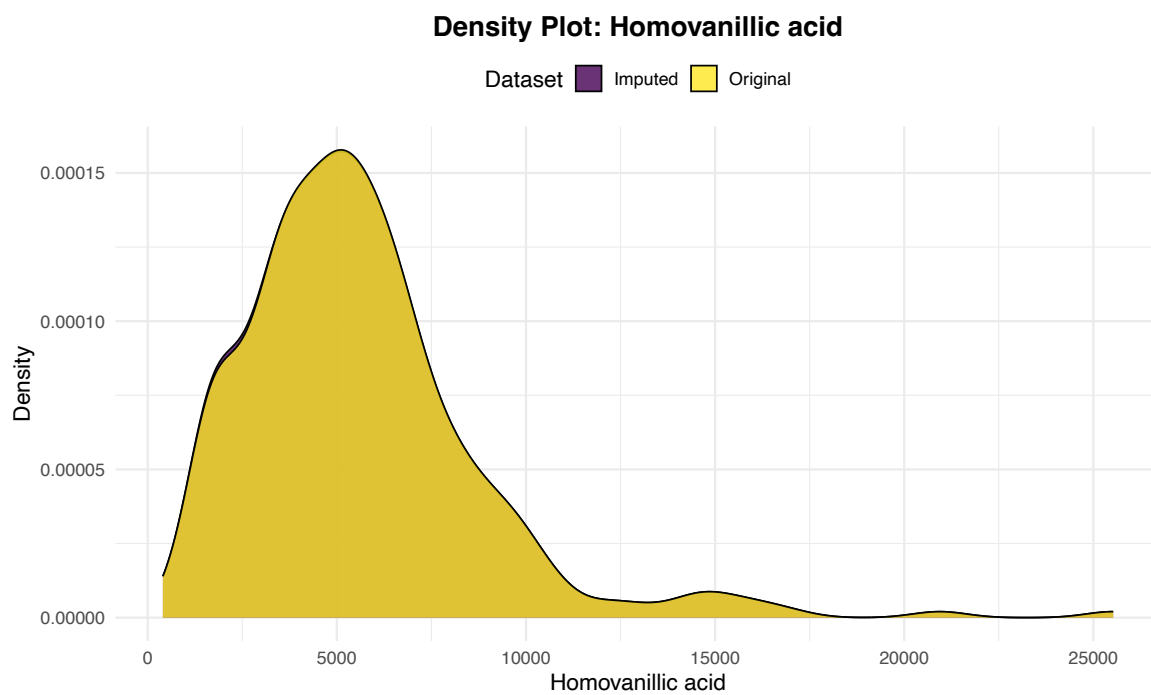


Density Plot: Catechol sulfate_1

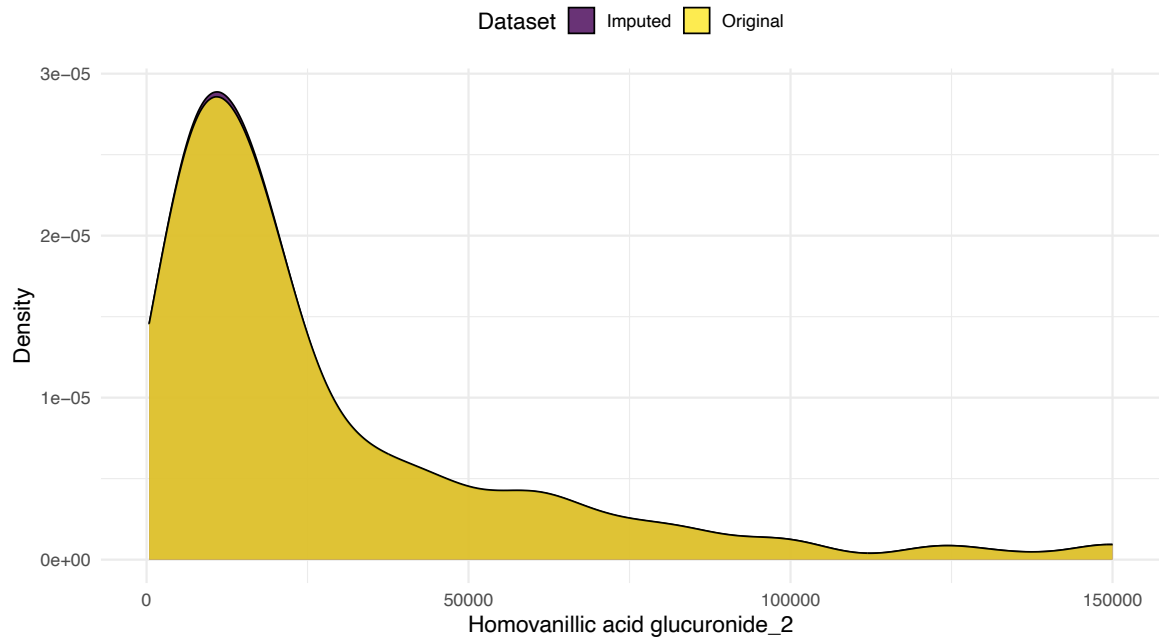


Density Plot: Vanillic acid glucuronide

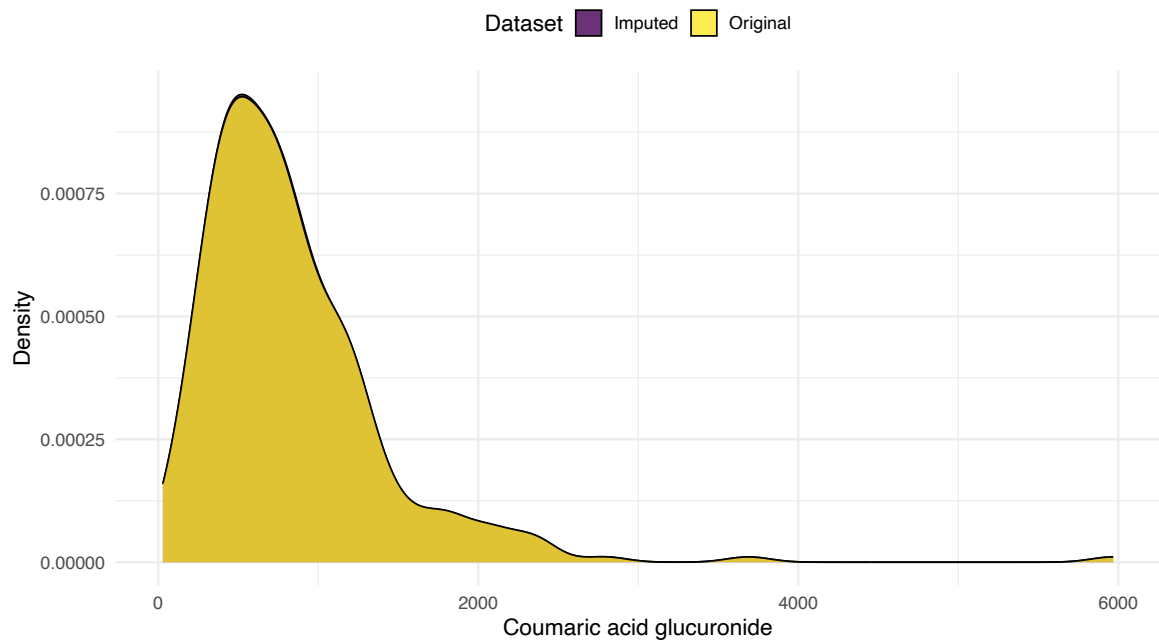




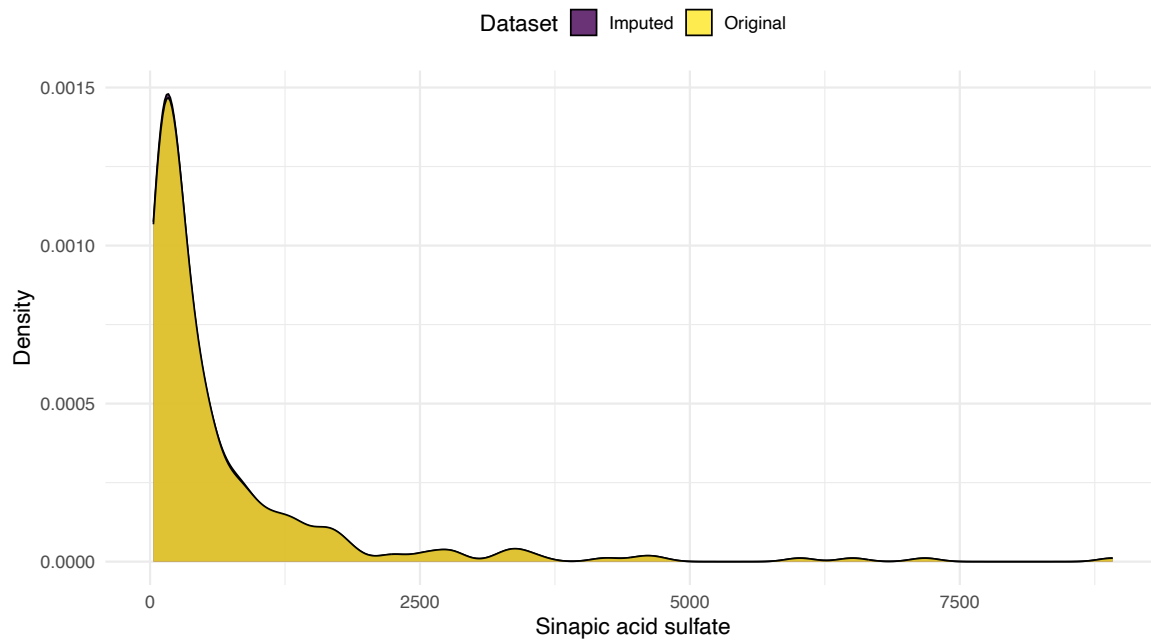
Density Plot: Homovanillic acid glucuronide_2



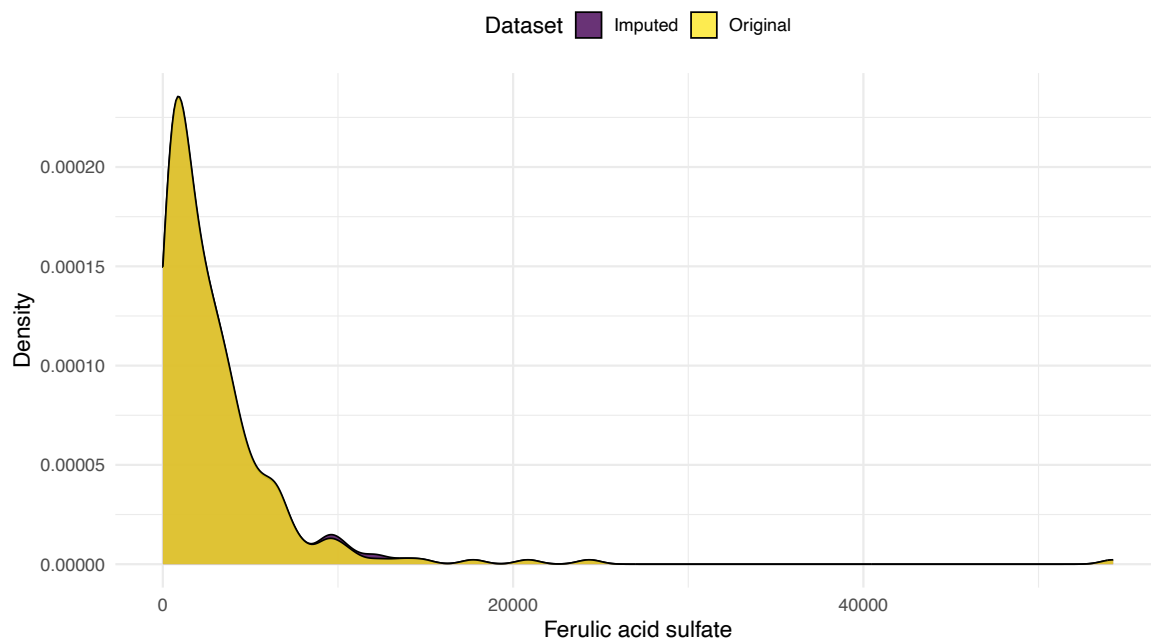
Density Plot: Coumaric acid glucuronide



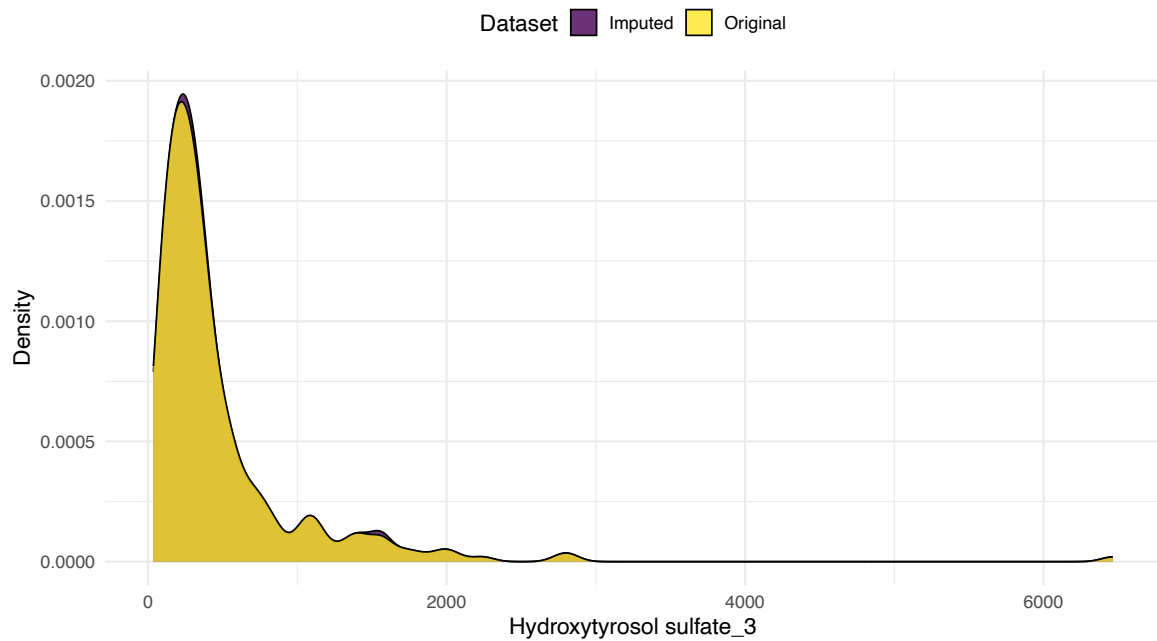
Density Plot: Sinapic acid sulfate



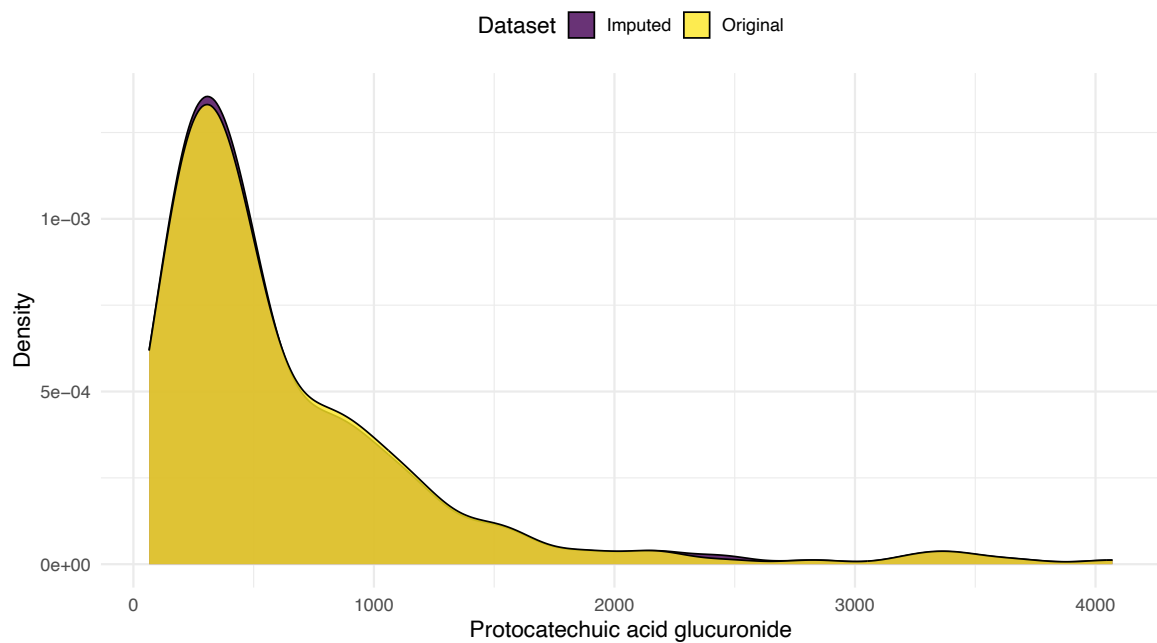
Density Plot: Ferulic acid sulfate



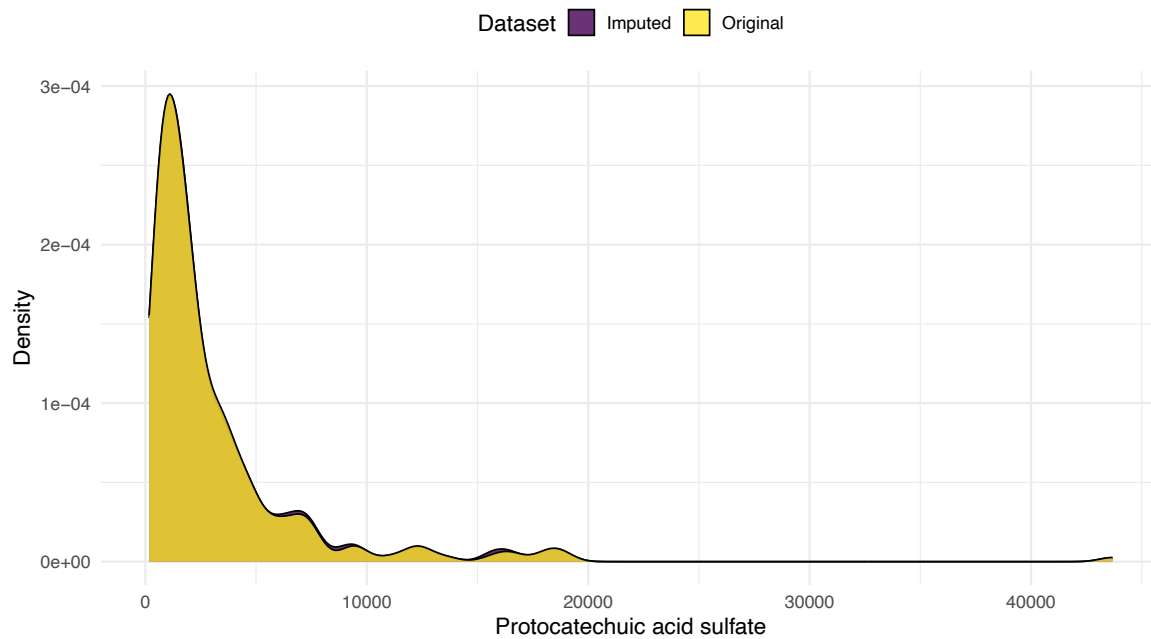
Density Plot: Hydroxytyrosol sulfate_3



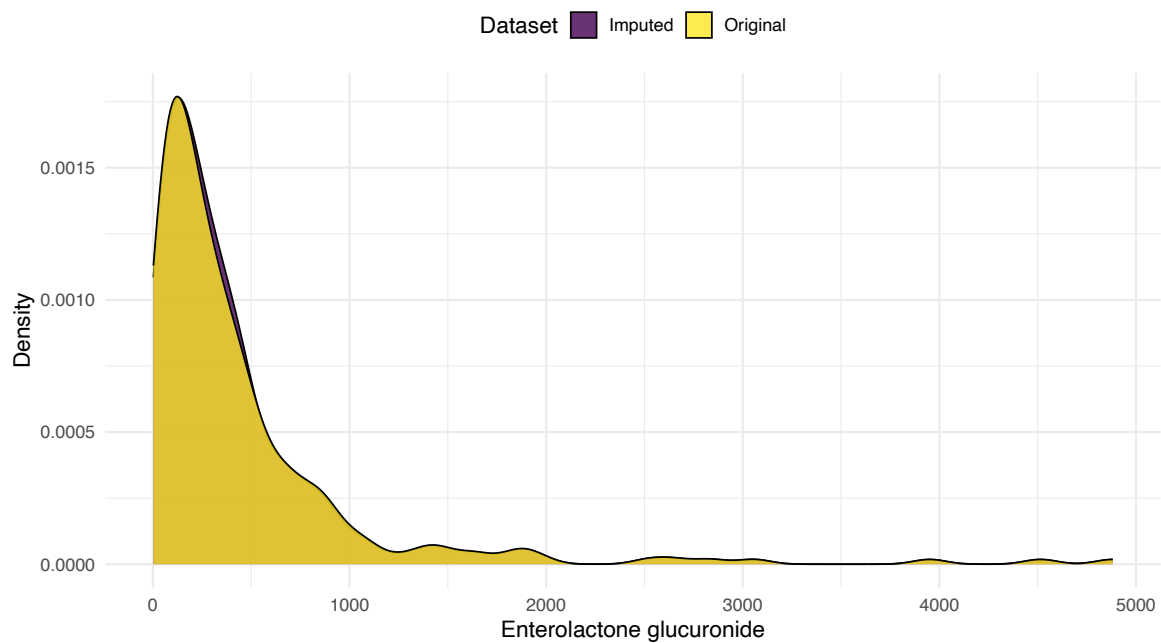
Density Plot: Protocatechuic acid glucuronide



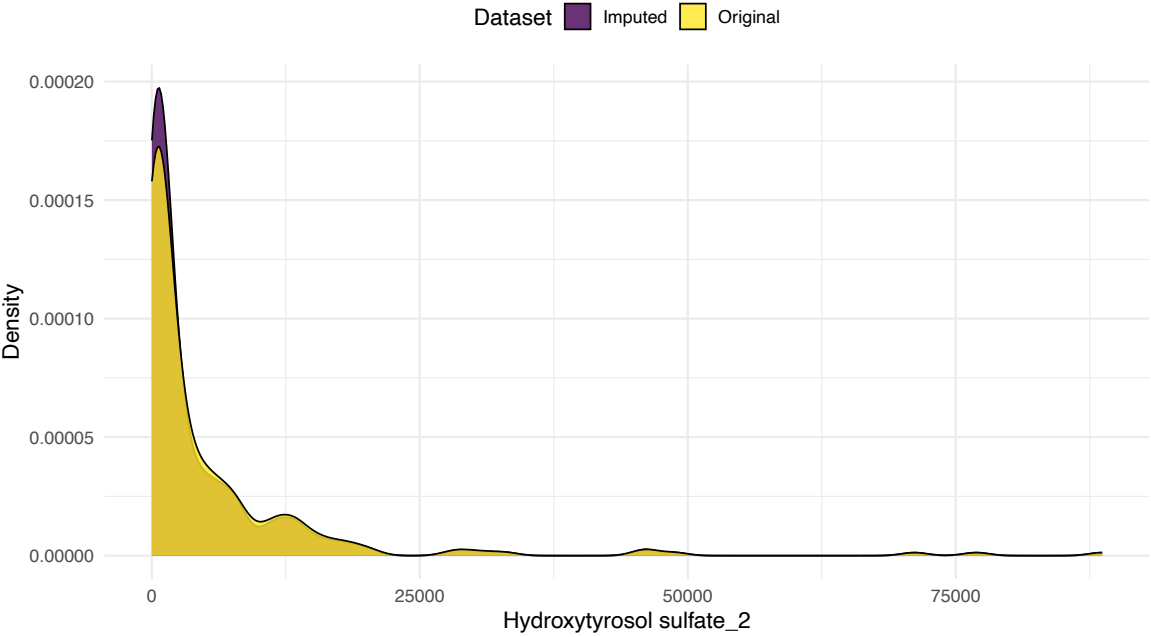
Density Plot: Protocatechuic acid sulfate



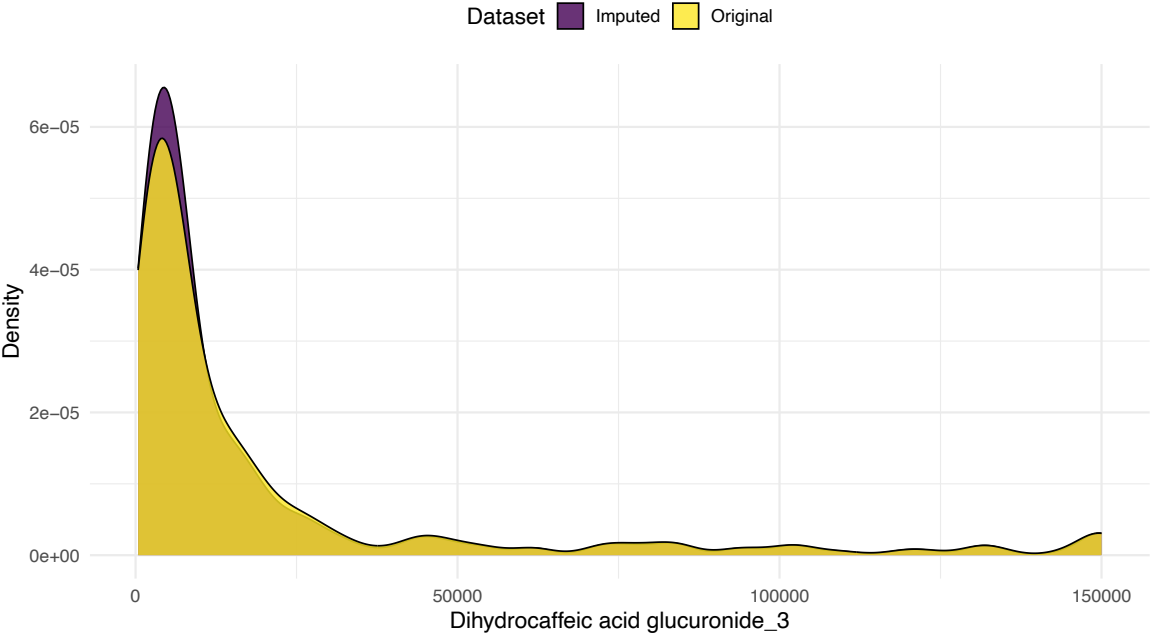
Density Plot: Enterolactone glucuronide



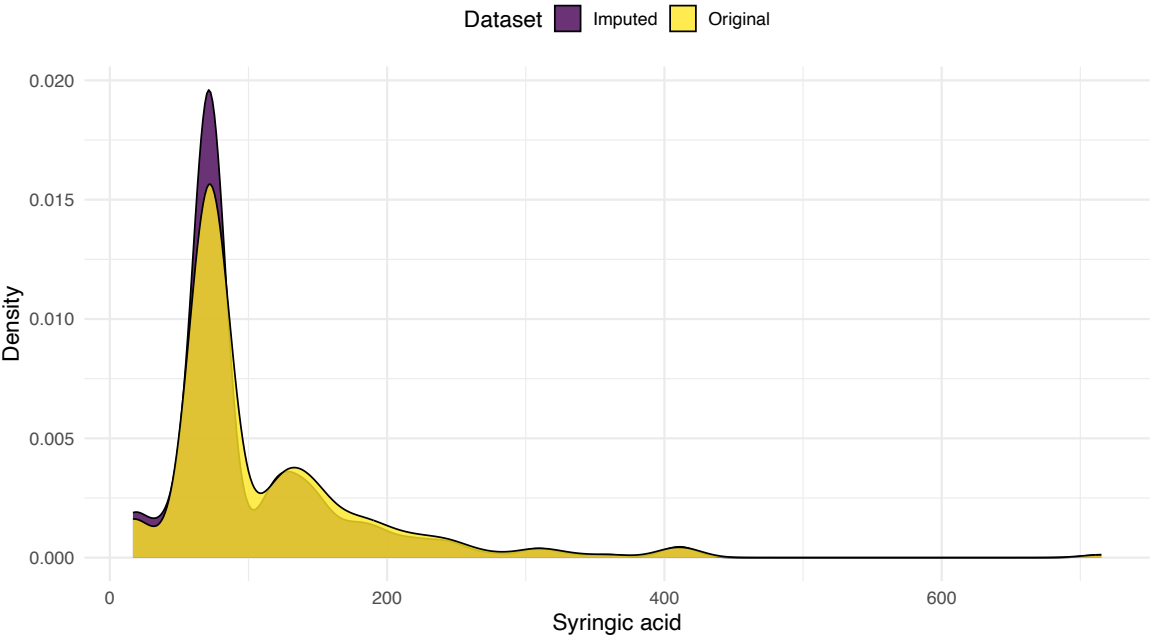
Density Plot: Hydroxytyrosol sulfate_2



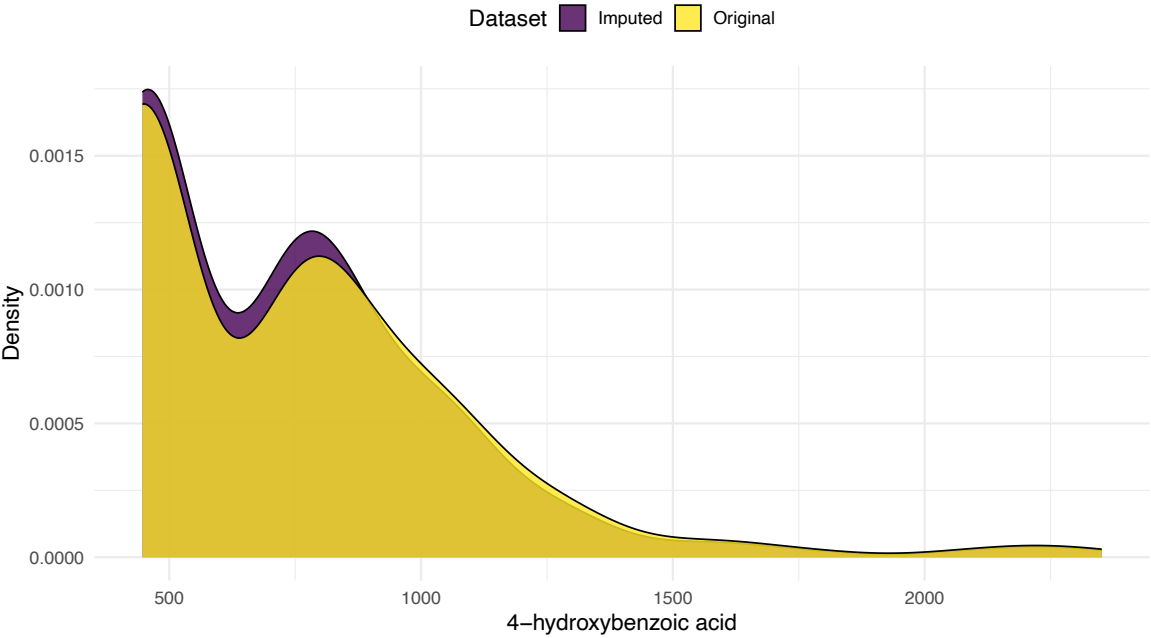
Density Plot: Dihydrocaffeic acid glucuronide_3



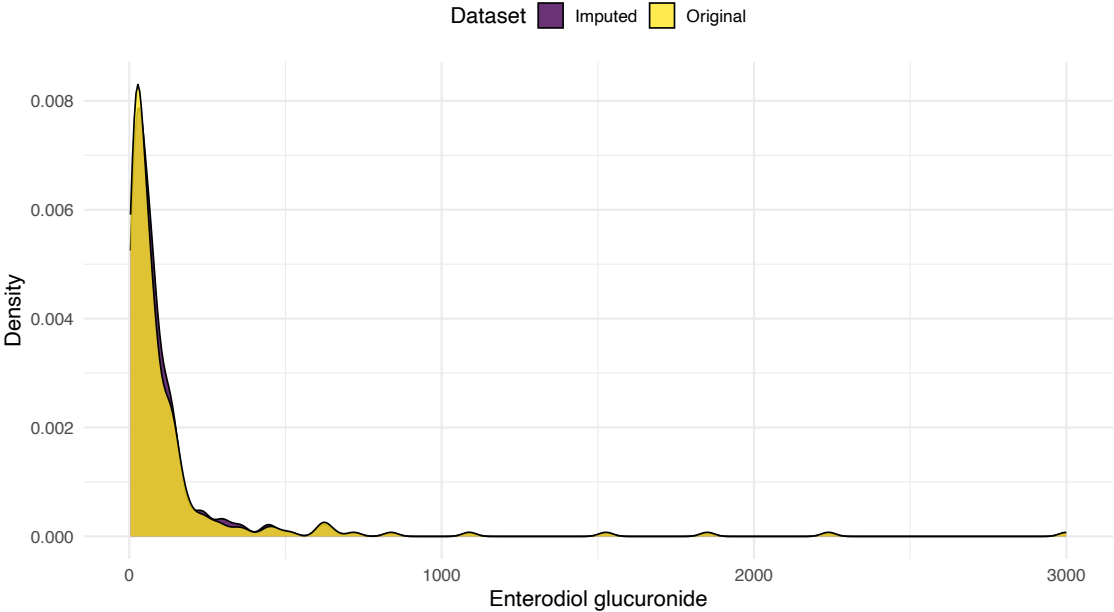
Density Plot: Syringic acid



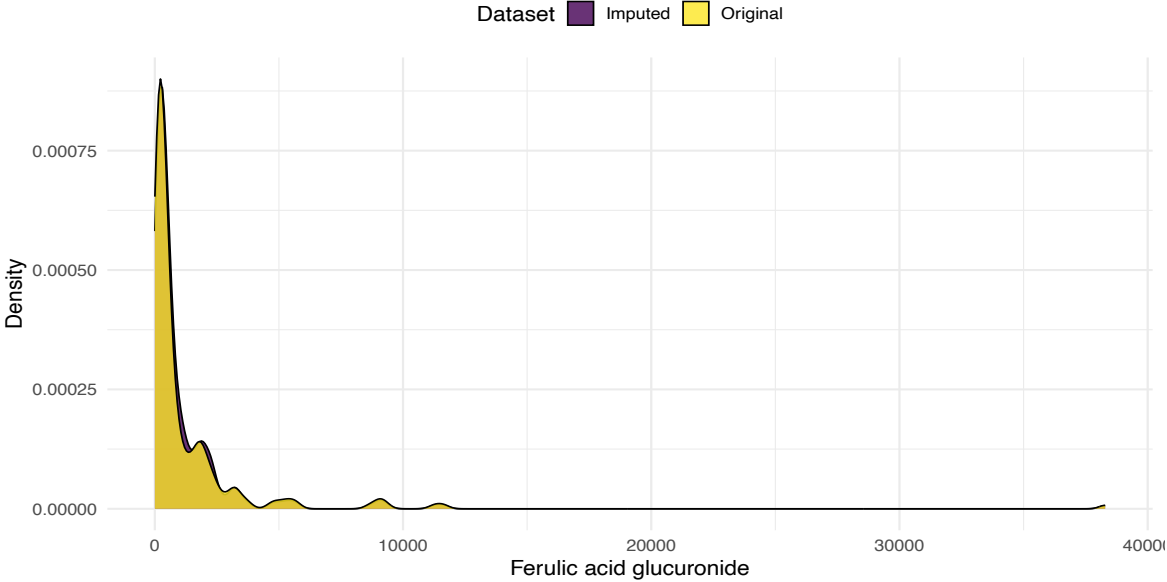
Density Plot: 4-hydroxybenzoic acid



Density Plot: Enterodiol glucuronide



Density Plot: Ferulic acid glucuronide



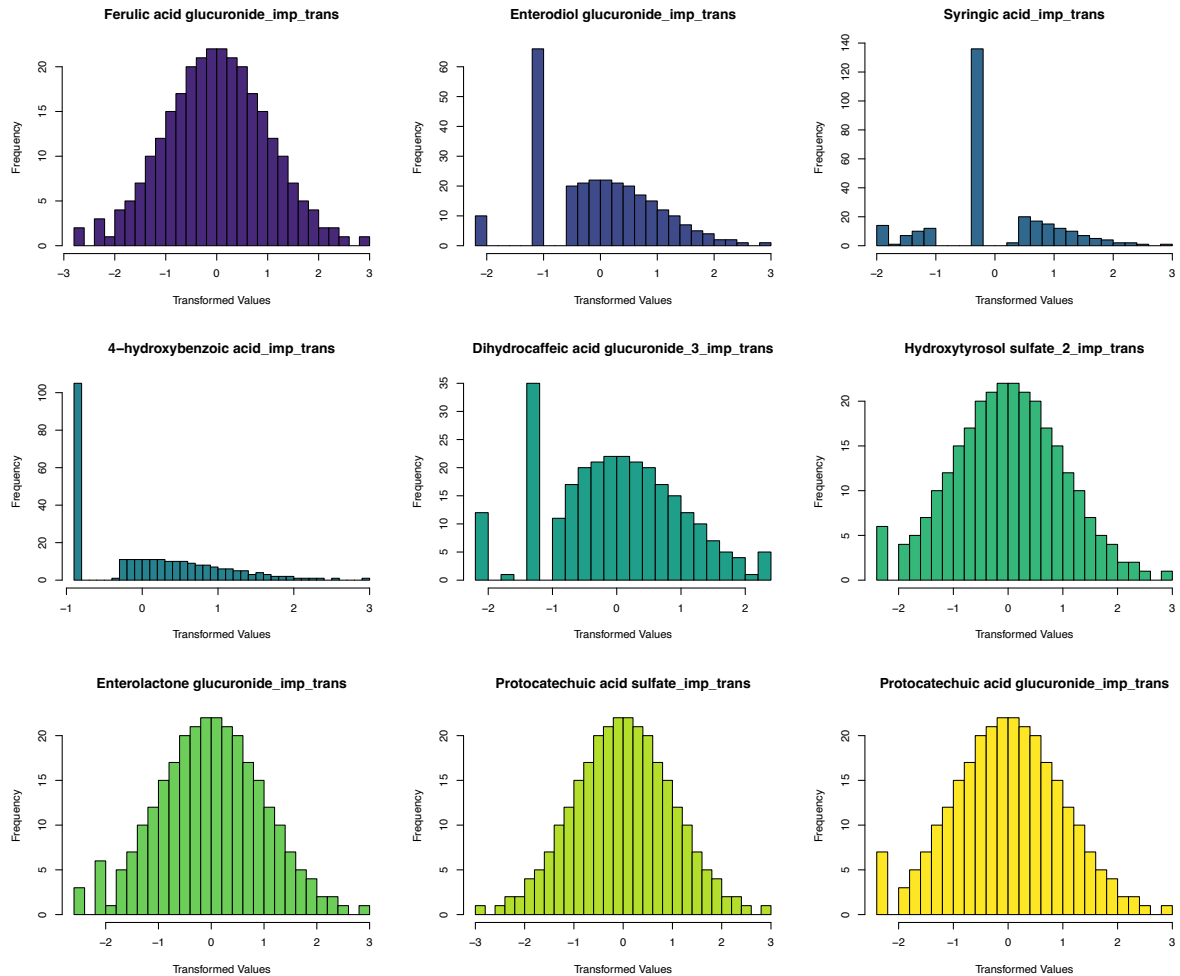
Comparison of Original and Imputed Data

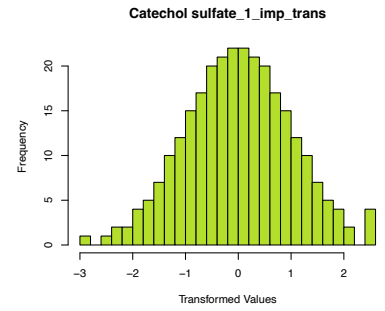
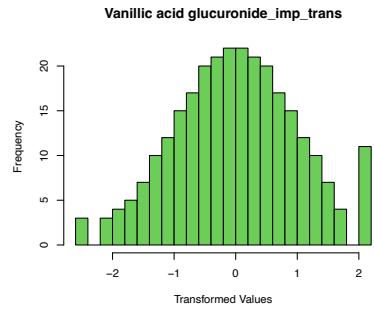
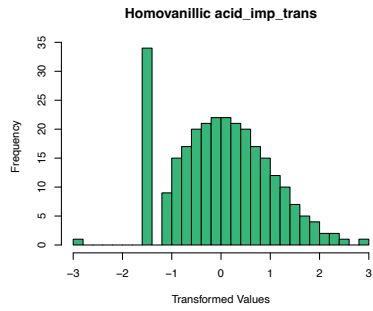
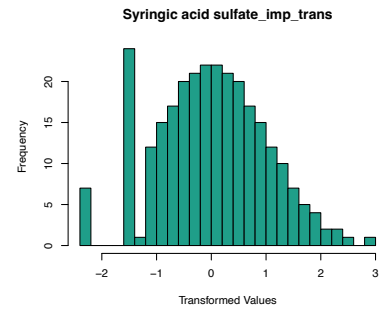
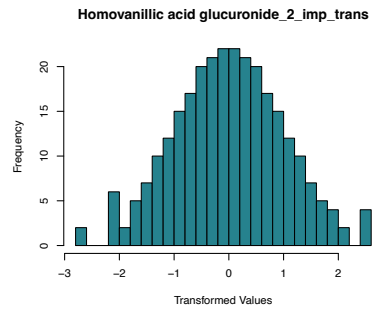
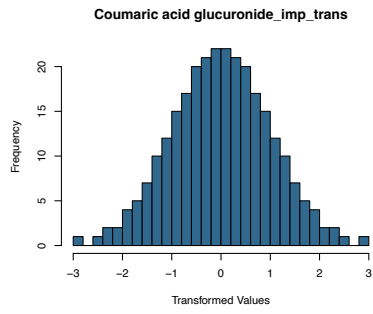
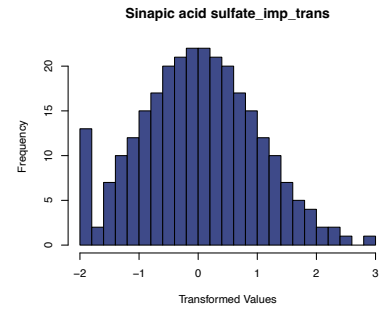
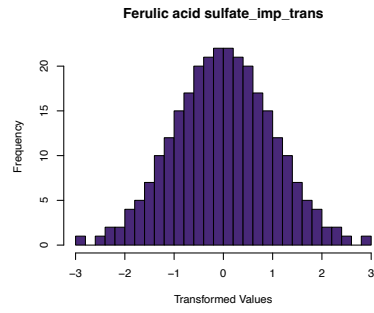
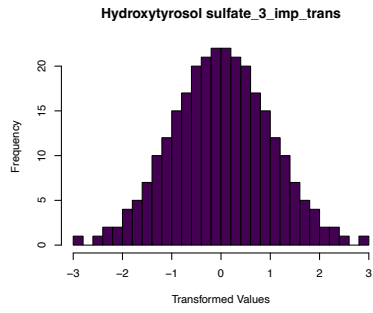
Numeric Variables

Variable	Original_Min	Original_1st_Qu	Original_Median	Original_Mean	Original_3rd_Qu	Original_Max	Original_Missing	Imputed_Min	Imputed_1st_Qu	Imputed_Median	Imputed_Mean	Imputed_3rd_Qu	Imputed_Max	Imputed_Missing
Ferulic acid glucuronide	2.442232	170.21357	381.75955	1225.9760	1221.9634	38286.7568	49/278	2.442232	197.45836	452.65112	1175.8871	1185.8629	38286.7568	0/278
Enterodiol glucuronide	4.200997	18.20432	53.32866	132.1915	117.2642	2999.2771	44/278	4.200997	18.20432	60.46852	128.6003	116.5153	2999.2771	0/278
Syringic acid	16.630668	72.06623	72.06623	111.3064	137.2168	715.0862	42/278	16.630668	72.06623	72.06623	104.5074	124.4765	715.0862	0/278
4-hydroxybenzoic acid	446.630725	446.63072	728.78191	743.2920	908.6182	2351.5341	37/278	446.630725	446.63072	719.62969	735.6288	888.8531	2351.5341	0/278
Dihydrocaffeic acid glucuronide_3	401.067510	3325.13485	6872.22177	20927.8375	17923.0508	150000.0000	27/278	401.067510	3368.04567	6649.24752	19487.9892	16619.8116	150000.0000	0/278
Hydroxytyrosol sulfate_2	10.565688	226.90316	1407.20047	5321.9732	5848.2238	88654.2028	24/278	10.565688	337.18352	1319.66349	4977.3055	5386.2379	88654.2028	0/278
Enterolactone glucuronide	2.442232	114.55306	258.38609	449.2315	496.8918	4881.3736	14/278	2.442232	122.38856	263.63281	443.3033	493.2952	4881.3736	0/278
Protocatechuic acid sulfate	171.425620	906.95682	1770.75850	3121.3164	3522.4496	43677.7640	14/278	171.425620	908.02832	1770.75850	3163.7818	3545.2179	43677.7640	0/278
Protocatechuic acid glucuronide	65.448419	263.74786	438.57213	645.4732	840.5170	4070.5876	10/278	65.448419	262.40850	436.69734	642.0564	835.4337	4070.5876	0/278
Hydroxytyrosol sulfate_3	35.661776	182.03783	307.15351	478.1321	526.9170	6463.4748	7/278	35.661776	185.39151	306.93921	478.3609	521.1297	6463.4748	0/278
Ferulic acid sulfate	2.442232	790.54960	1896.06339	3051.6228	3787.9340	54260.1762	5/278	2.442232	803.95795	1901.22389	3090.6892	3844.0228	54260.1762	0/278
Sinapic acid sulfate	30.857576	125.34319	269.76569	678.7212	721.6029	8916.3399	4/278	30.857576	125.34319	269.21153	673.2034	721.6029	8916.3399	0/278
Coumaric acid glucuronide	29.046543	453.76477	707.59124	835.6474	1075.0555	5968.0369	2/278	29.046543	455.20251	707.59124	834.7120	1072.8565	5968.0369	0/278
Homovanillic acid glucuronide_2	401.067510	8267.74987	16760.63008	28384.3828	37407.3640	150000.0000	2/278	401.067510	8307.27034	16688.14085	28270.7683	37282.4350	150000.0000	0/278
Syringic acid sulfate	16.630668	181.33986	343.41723	497.1872	534.7045	5334.4058	2/278	16.630668	176.87088	340.01571	494.4168	533.5010	5334.4058	0/278
Homovanillic acid	401.067510	3560.87032	5180.62575	5629.8484	6828.0149	25523.6265	1/278	401.067510	3559.42443	5172.63554	5617.8377	6825.1096	25523.6265	0/278
Vanillic acid glucuronide	14.326718	719.29259	1934.26040	15748.9626	8856.2387	150000.0000	1/278	14.326718	722.79736	1936.03251	15713.3136	8839.0470	150000.0000	0/278
Catechol sulfate_1	156.220579	10597.10248	18519.05273	28530.9496	35471.2996	150000.0000	0/278	156.220579	10597.10248	18519.05273	28530.9496	35471.2996	150000.0000	0/278
Dihydrocaffeic/Homovanillic sulfate	401.067510	19483.26672	41827.67731	51551.9022	72500.8219	150000.0000	0/278	401.067510	19483.26672	41827.67731	51551.9022	72500.8219	150000.0000	0/278

Section 3: Inverse Normal Transformation of Imputed Polyphenols

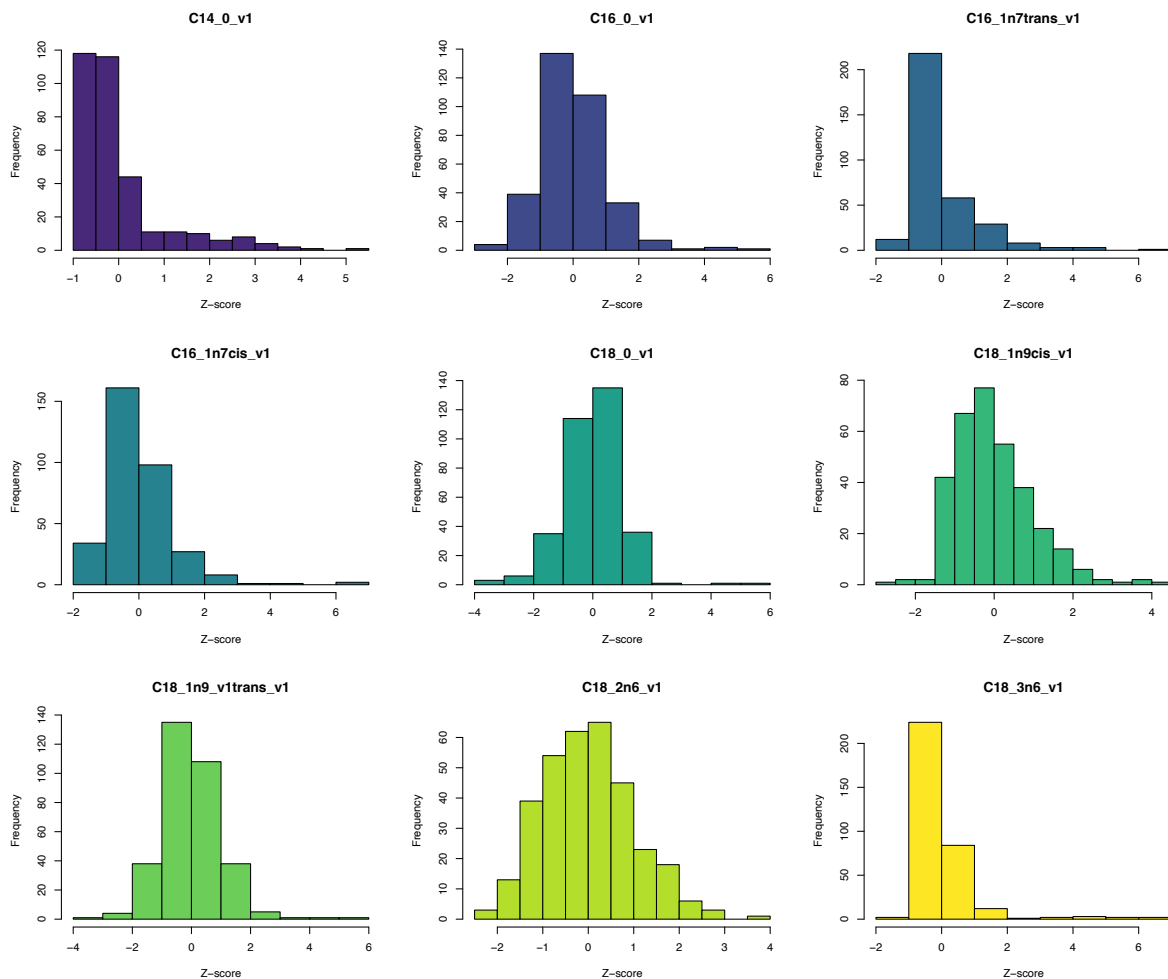
The histograms presented below illustrate the resulting distributions, reflecting the standardised values used in downstream analyses.

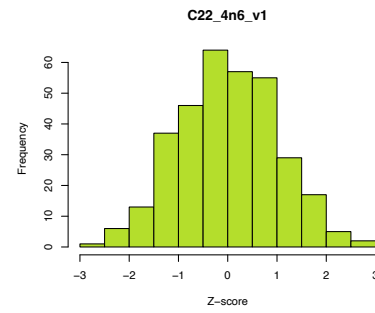
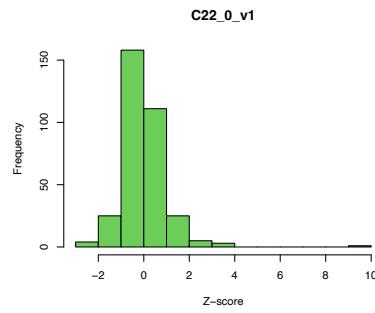
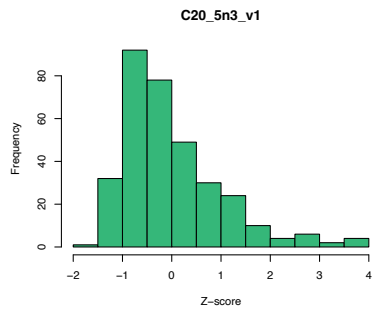
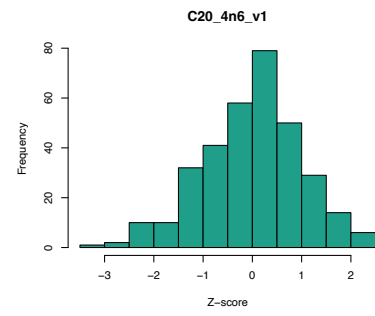
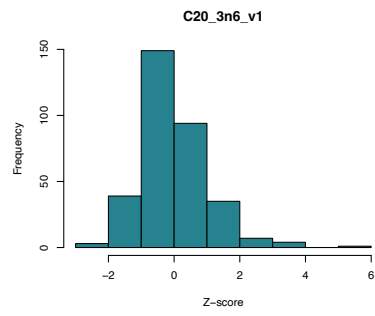
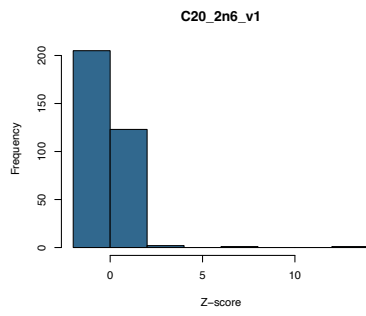
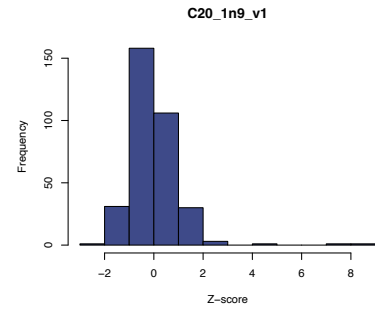
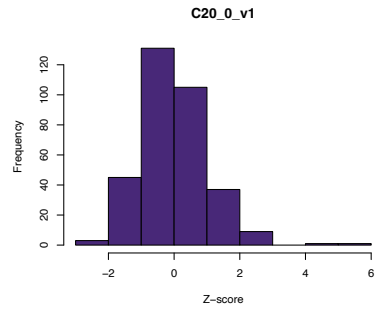
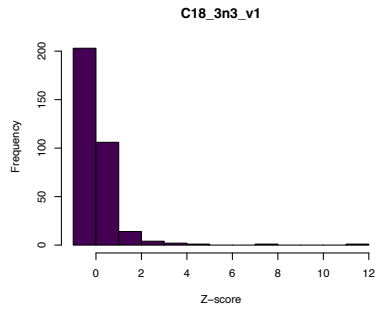


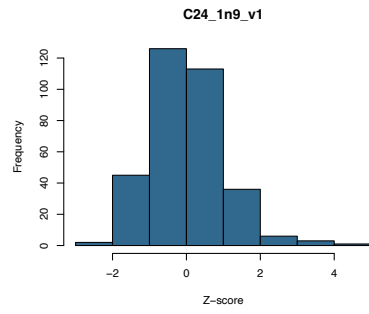
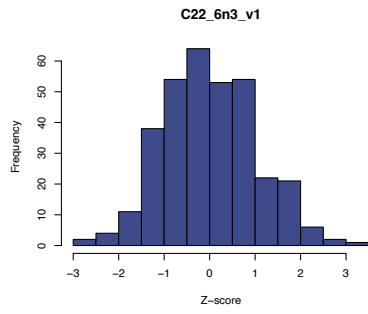
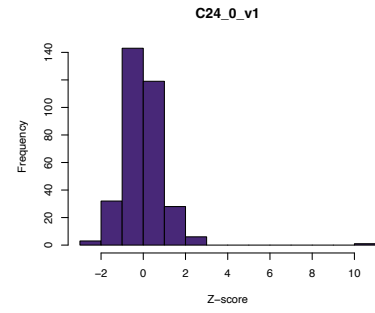
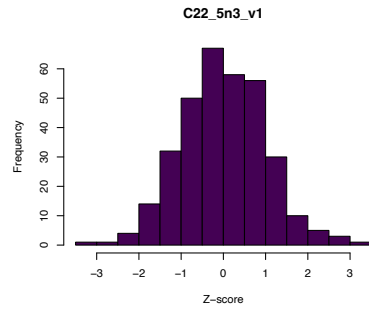
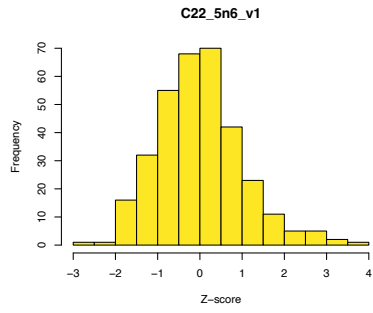


Section 4: Z-Score Normalisation of RBC Fatty Acid Data

The histograms presented below illustrate the resulting distributions, reflecting the standardised values used in downstream analyses.

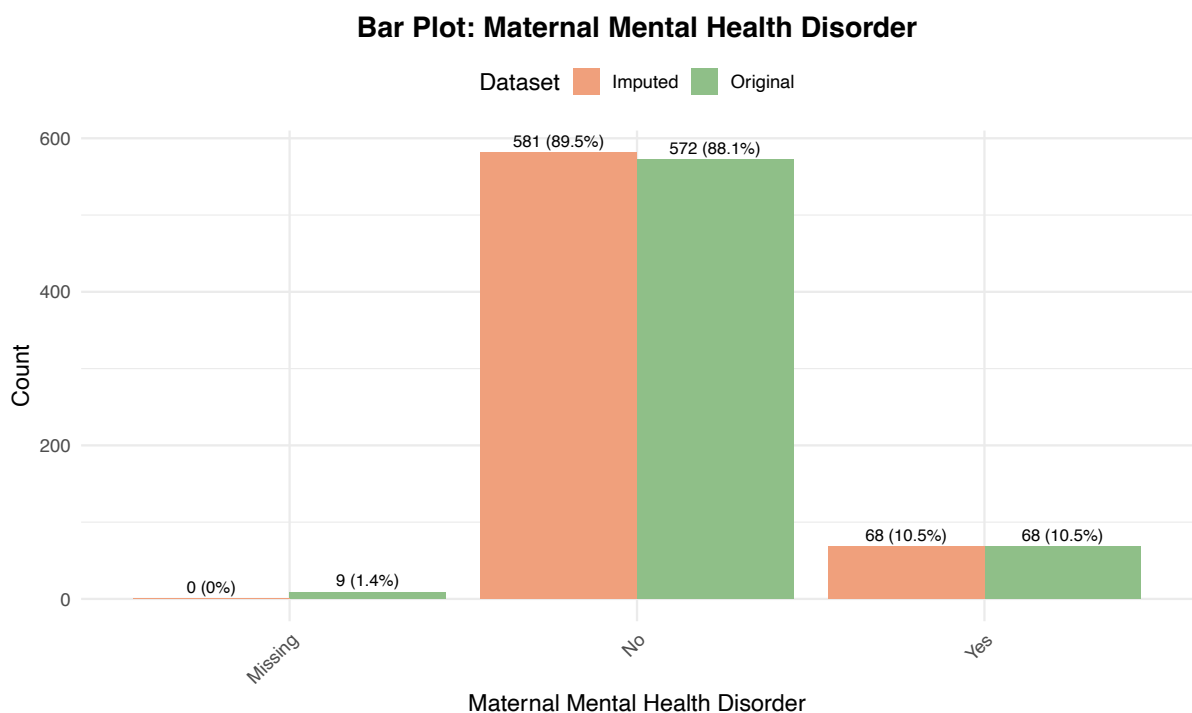
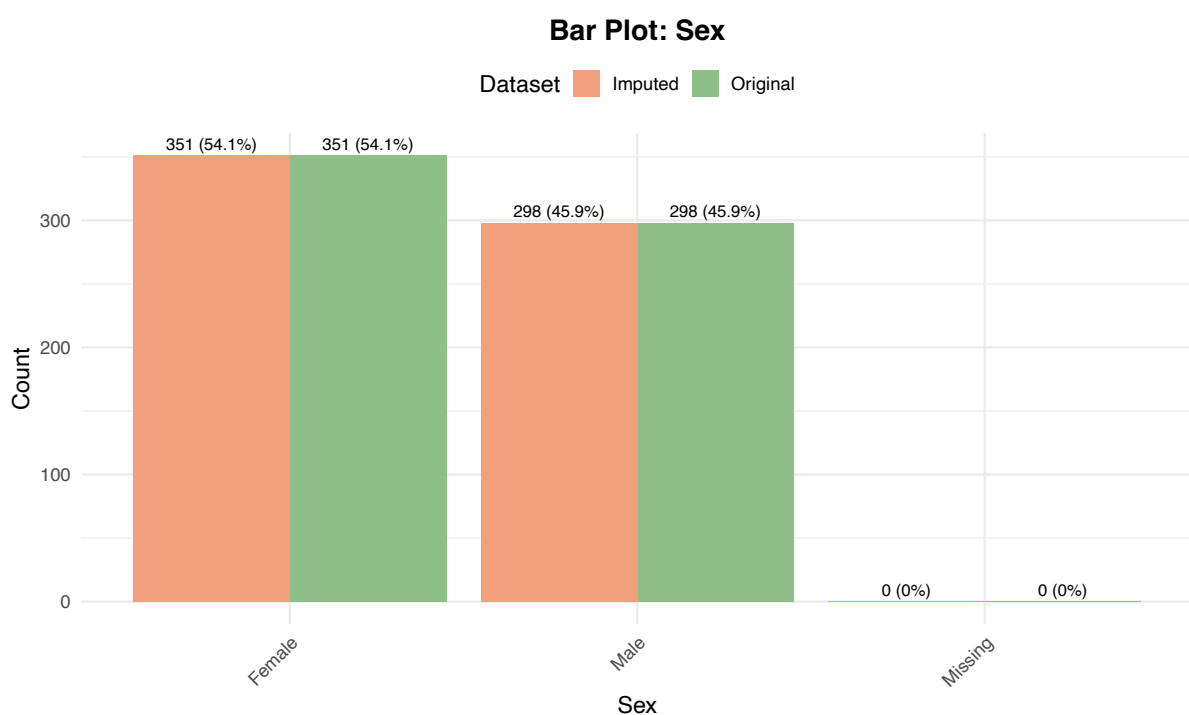




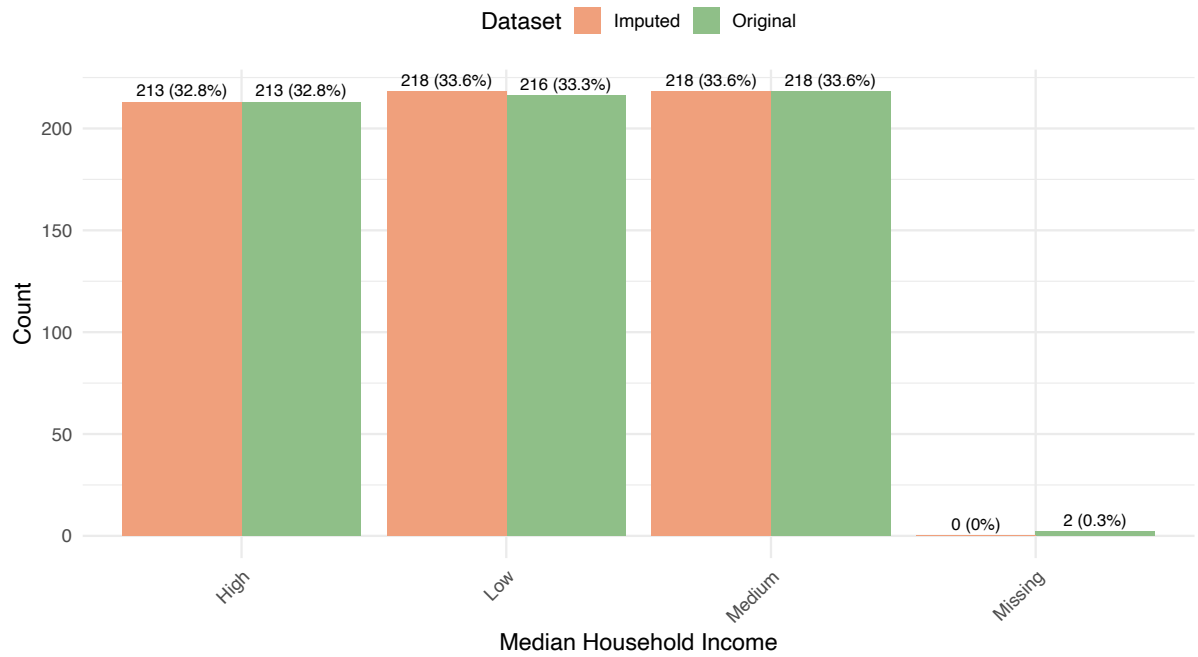


Section 5: Inspection and Quality Control of Covariate Imputation

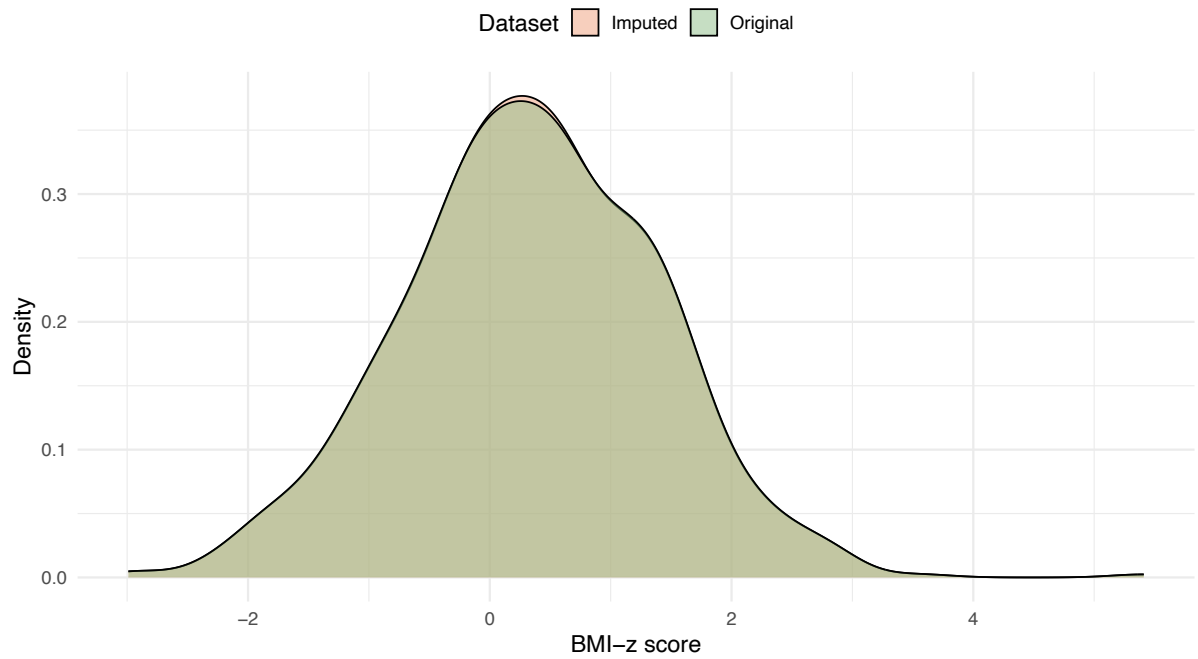
The quality of imputation was evaluated by visually comparing the distributions of original and imputed values for each covariate and through quantitative assessment of imputation accuracy. Plots display side-by-side comparisons of the observed and imputed data for each variable included in the analysis. Additionally, objective imputation performance metrics were calculated to quantify the accuracy of the imputation process for both numeric and categorical variables.



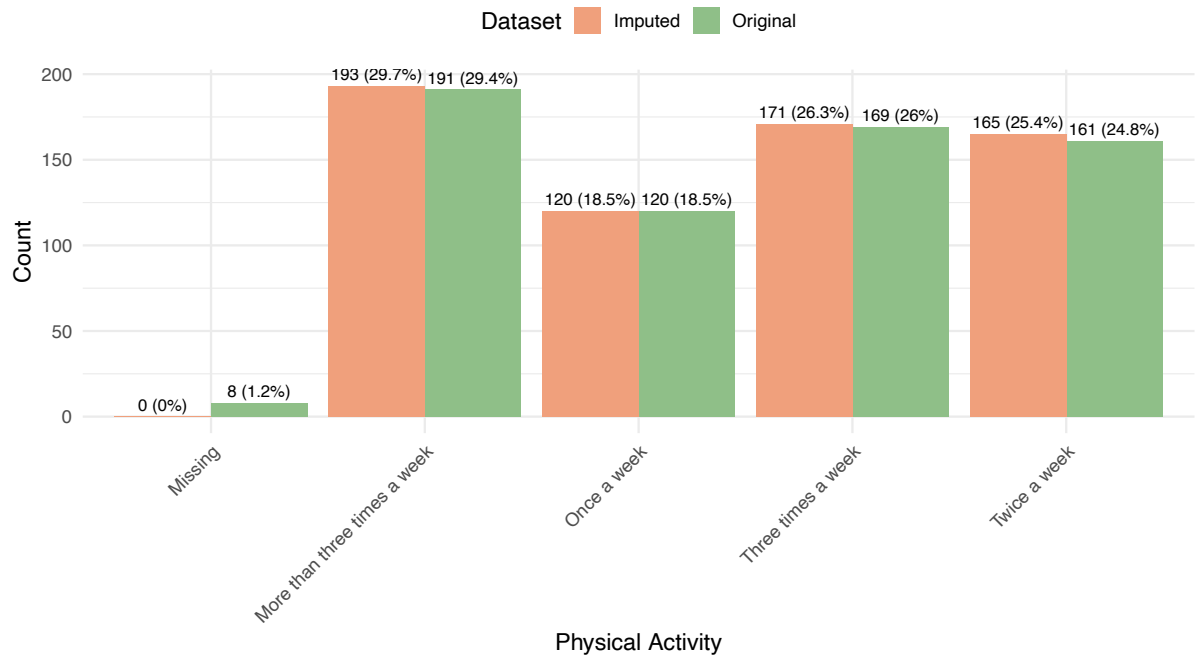
Bar Plot: Median Household Income



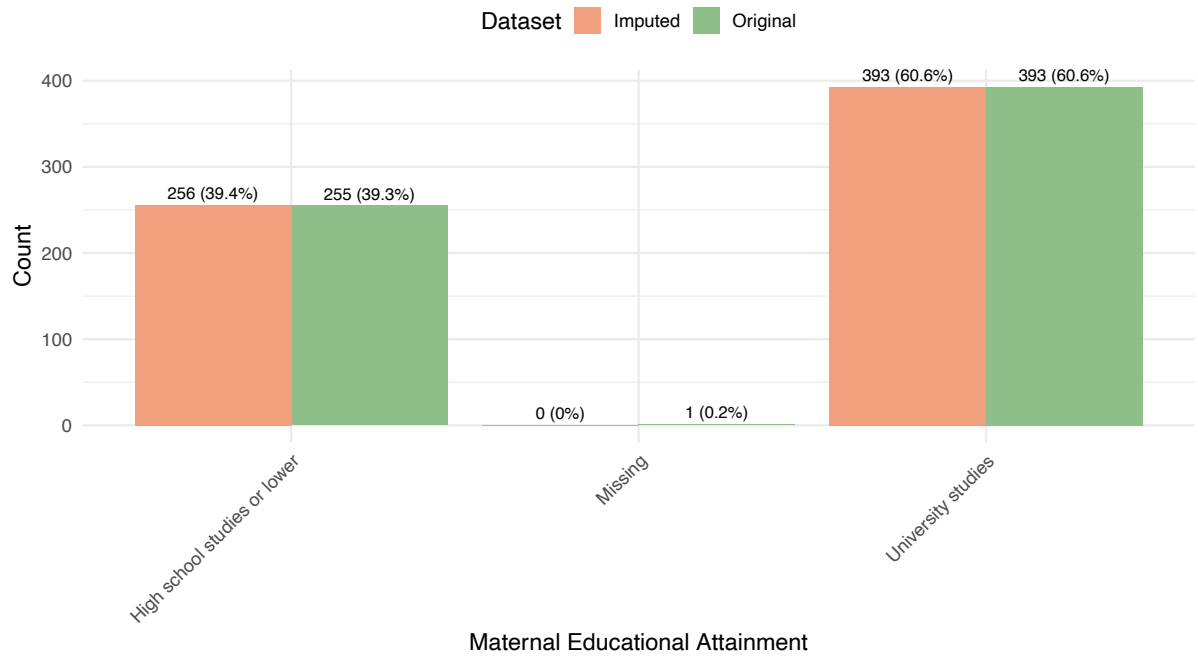
Density Plot: BMI-z score



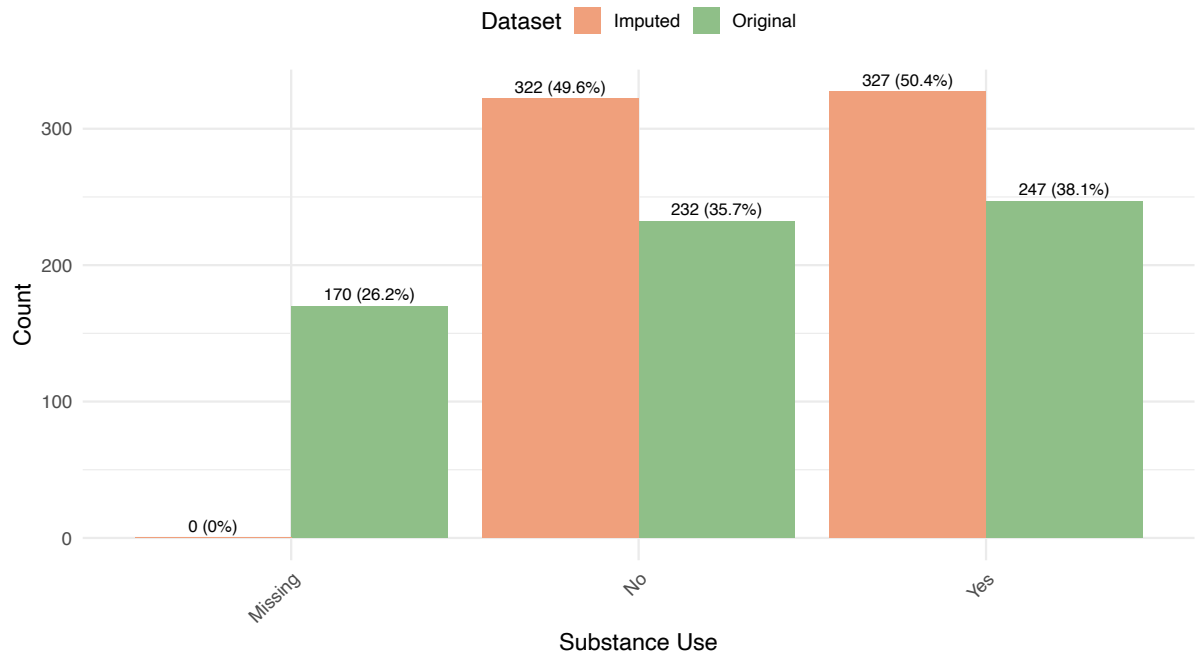
Bar Plot: Physical Activity



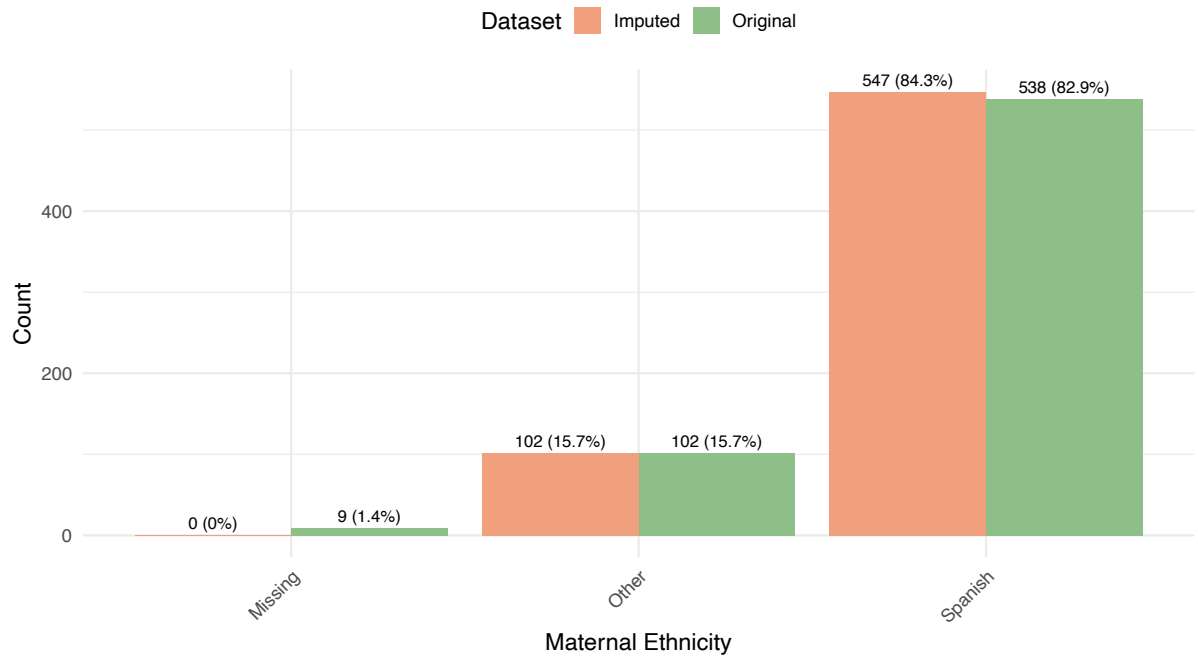
Bar Plot: Maternal Educational Attainment

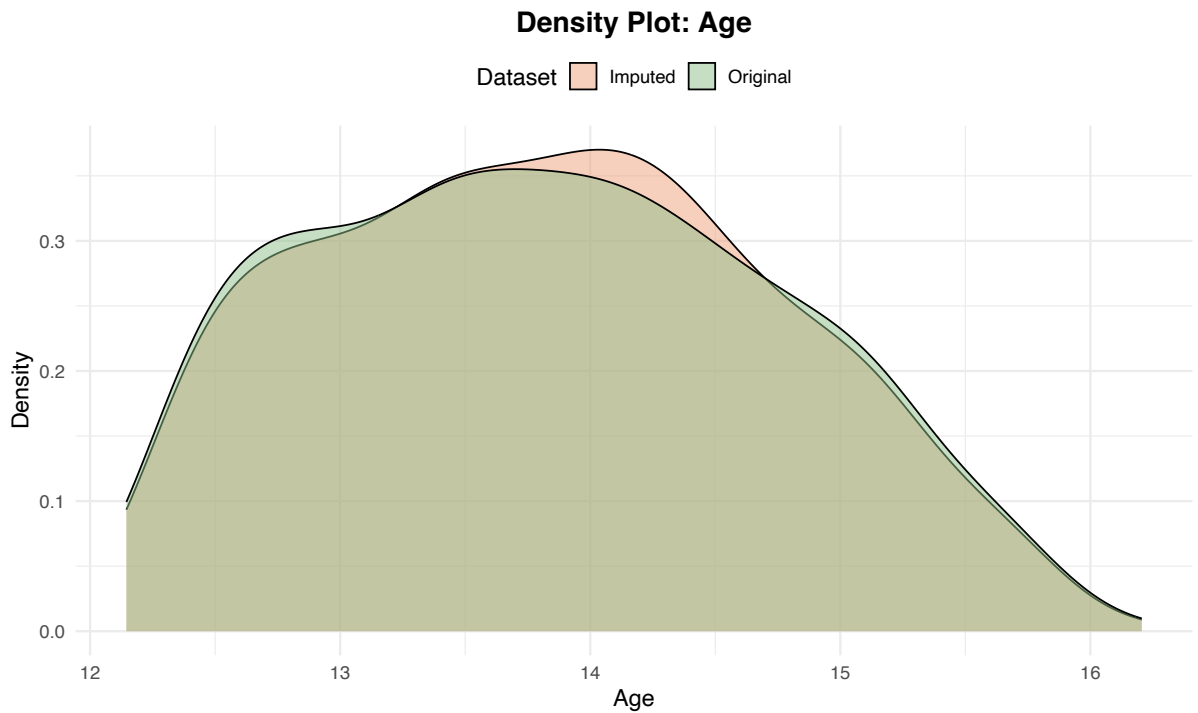


Bar Plot: Substance Use



Bar Plot: Maternal Ethnicity





Comparison of Original and Imputed Data

Numeric Variables

Variable	Original (Min)	Original (1st Qu.)	Original (Median)	Original (Mean)	Original (3rd Qu.)	Original (Max)	Original (Missing)	Imputed (Min)	Imputed (1st Qu.)	Imputed (Median)	Imputed (Mean)	Imputed (3rd Qu.)	Imputed (Max)	Imputed (Missing)
idnum	21101.00	53508.0000	123112.00	123506.0000	181205.0000	203306.00	0	21101.00	53508.00	123112.00	123506.0000	181205.00	203306.00	0
kidmed_score_v1	-1.00	5.0000	7.00	6.8040	8.0000	12.00	0	-1.00	5.00	7.00	6.8040	8.00	12.00	0
bmiAgeZ	-2.99	-0.3275	0.33	0.3403	1.0975	5.41	3	-2.99	-0.32	0.33	0.3402	1.09	5.41	0
age_neuro_v1	12.15	13.0600	13.78	13.8300	14.5300	16.21	31	12.15	13.10	13.83	13.8400	14.49	16.21	0

Categorical Variables

Variable	Original (Levels)	Original (Missing)	Imputed (Levels)	Imputed (Missing)
sex	Male: 298, Female: 351	0	Male: 298, Female: 351	0
mother_country_cat	Spanish: 538, Other: 102	9	Spanish: 547, Other: 102	0
substance_use_v1	No: 232, Yes: 247	170	No: 322, Yes: 327	0
mother_studies_Final	High school: 255, University: 393	1	High school: 256, University: 393	0
physical_activity_freq	Once: 120, Twice: 161, Three: 169, More: 191	8	Once: 120, Twice: 165, Three: 171, More: 193	0
income_tertiles	Low: 216, Medium: 218, High: 213	2	Low: 218, Medium: 218, High: 213	0
mother_mental_disorder	No: 572, Yes: 68	9	No: 581, Yes: 68	0

Imputation Metrics

NRMSE (numeric) 0.1440*

PFC (categorical) 0.3435*

* Lower values indicate better accuracy