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DISSERTATION

“The effects of dietary intake on cognitive functioning, wellbeing, and the brain”
Die Auswirkungen der Ernährung auf kognitive Funktionen, Wohlbefinden und das Gehirn

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Abstract

The nutritional content of the food we consume affects several metabolic pathways that can impact the brain, and thereby cognitive functioning and wellbeing. This thesis aimed to investigate to what extent dietary intake affects cognitive functioning and wellbeing and elucidate underlying mechanisms using a literature review and an online observation study. Study 1, a literature review, showed that dietary macronutrients – carbohydrates, fatty acids, and proteins – impact acute and long-term cognitive functioning as well as neural correlates in healthy adults. A framework is proposed based on existing findings indicating that glucose and insulin metabolism, neurotransmitter actions, and oxidation/inflammation are among the primary mechanisms linking dietary macronutrient intake, brain functioning, and -integrity.

Study 2 investigated lifestyle factors and mental wellbeing of healthy human adults during the COVID-19 pandemic and found that fruit/ vegetable intake, alongside physical activity and high-quality social interactions, predicted daily wellbeing. Together, these studies confirm the critical role that dietary intake plays in cognitive and affective functioning in healthy human adults. A follow-up study is proposed to further investigate to what extent habitual diet affects glucose and neurotransmitter metabolism and subsequent brain function in a controlled laboratory setting. Finally, clinical implications are suggested in the context of improving cognitive health outcomes in an elderly population.

Zusammenfassung

Der Nährstoffgehalt der von uns verzehrten Lebensmittel beeinflusst verschiedene Stoffwechselwege, die sich auf das Gehirn und damit auf die kognitive Leistungsfähigkeit und das Wohlbefinden auswirken. Ziel dieser Arbeit war es zu untersuchen, inwieweit sich die Nahrungsaufnahme auf die kognitive Leistungsfähigkeit und das Wohlbefinden auswirkt, und die zugrunde liegenden Mechanismen anhand einer Literaturübersicht und einer Online-Beobachtungsstudie zu klären. Studie 1, eine Literaturübersicht, zeigte, dass Makronährstoffe - Kohlenhydrate, Fettsäuren und Proteine - die akute und langfristige kognitive Funktion sowie die neuronalen Korrelate bei gesunden Erwachsenen beeinflussen. Auf der Grundlage bestehender Erkenntnisse wird ein Rahmenwerk vorgeschlagen, das

zeigt, dass der Glukose- und Insulinstoffwechsel, die Wirkung von Neurotransmittern und die Oxidation/Entzündung zu den wichtigsten Mechanismen gehören, die die Aufnahme von Makronährstoffen, die Gehirnfunktion und -integrität miteinander verbinden.

Studie 2 untersuchte Lebensstilfaktoren und das psychische Wohlbefinden gesunder erwachsener Menschen während der COVID-19-Pandemie und stellte fest, dass der Verzehr von Obst und Gemüse das tägliche Wohlbefinden vorhersagt. Zusammen bestätigen diese Studien die entscheidende Rolle, die die Nahrungsaufnahme für die kognitive und affektive Leistungsfähigkeit gesunder Erwachsener spielt. Es wird eine Folgestudie vorgeschlagen, um weiter zu untersuchen, inwieweit die gewohnheitsmäßige Ernährung den Glukose- und Neurotransmitter-Stoffwechsel und damit die Gehirnfunktion in einer kontrollierten Laborumgebung beeinflusst. Schließlich werden klinische Implikationen im Zusammenhang mit der Verbesserung der kognitiven Gesundheit älterer Menschen diskutiert.

1 Introduction

We all need to eat to nourish and fuel our bodies. A healthy diet positively affects physical (Alhazmi et al., 2014) and mental health (Sarris et al., 2015; Solfrizzi et al., 2017). However, the rise of obesity in the industrialized world (Chooi et al., 2019) attests to the fact that an increasing number of people consume inadequate diets. Moreover, high comorbidity rates of obesity with diabetes, dementia and depression (Corfield et al., 2016; Faith et al., 2002; Holt et al., 2014) warrant a closer examination of diet and brain function.
The following paragraphs will argue why studying diet together with cognitive and mental health measures is crucial, followed by an introduction to the methods of studying dietary intake and macronutrients. Finally, food consumption is not isolated from other health behaviors. Instead, other lifestyle factors co-vary and should be considered when studying dietary impact in relation to brain function and mental health (Walsh, 2011).

1.1 Nutrition to support cognitive functioning

The brain coordinates vital bodily functions, deals with sensory input, computes cognitive responses, and gives rise to or controls emotions and moods. The use of nutrition to enhance cognitive functions has raised interest in various fields, from student performance (Taras, 2005) to military applications (Lieberman, 2003). Importantly, dietary components and nutritional interventions seem to have distinct effects on particular cognitive functions (Lieberman, 2003). For example, dietary tyrosine maintains cognitive function under stressful conditions such as high task demands or physical stress (induced by extreme temperatures or sleep deprivation) (Hase et al., 2015). However, many of the existing studies about the effects of macronutrients are contradictory and have methodological shortcomings (Lieberman, 2003). Therefore, further research investigating how macronutrients affect cognitive performance is needed (Lieberman, 2003).

1.2 Dietary interventions for mental health

Mental health disorders place an enormous burden on individuals and society at large (Vigo et al., 2016). Most recently, the COVID-19 pandemic[1] has highlighted the need to support people experiencing mental health crises as it has taken a considerable toll on mental health globally (Collaborators et al., 2021). High infection rates and restrictions to limit the spread of the virus, such as contact restrictions, were associated with increased prevalence of depression and anxiety, with women and young people among the most affected (Collaborators et al., 2021). Strategies to promote mental wellbeing (or "positive mental health") are critical to addressing the individual and societal burden posed by these mental health disorders (Collaborators et al., 2021).

The emerging field of nutritional psychiatry may offer one such approach; by focusing on diet as a modifiable risk factor (Marx et al., 2017; Owen and Corfe, 2017). However, there are conflicting results on whether certain dietary styles cause depression and anxiety (Lai et al., 2014; Quirk et al., 2013), emphasizing the need for randomized controlled trials to test dietary interventions' effectiveness (Adan et al., 2019). Moreover, many questions remain regarding underlying metabolic and cellular mechanisms (Adan et al., 2019). Finally, a better understanding of which dietary components are beneficial for mental health could guide dietary interventions (Gibson-Smith et al., 2020).

In sum, diet seems to be a promising avenue for reducing the burden posed by mental health diseases and obesity, and other lifestyle diseases. However, many questions remain unanswered about which diets and dietary components affect brain function and their underlying mechanisms.

1.3 Studying dietary intake

Dietary impact can be studied using experimental and observational methods. Experimental designs include dietary interventions and acute administration of dietary components. Dietary interventions may manipulate or supplement specific dietary components

1 COVID-19 refers to coronavirus disease, which first broke out at the end of 2019 (Velavan and Meyer, 2020). Since then it has spread across the world, with a total of over 260 million cases worldwide and a death toll of over 5 million (worldometers.info, accessed on 27 November 2021).

and allow testing the effect over time. For example, a large randomized controlled trial where older adults received folic acid and a vitamin B-12 supplement showed improved memory function after 24 months (Walker et al., 2012).

Acute administration of meals or supplements allows testing of short-term effects while promoting a particular nutrient's presence (or absence) in the body. Strang and colleagues used this method; participants consumed two breakfasts with varying macronutrient compositions in a randomized order (separated by at least seven days) (Strang et al., 2017). The authors showed that the different carbohydrate-protein ratios of the breakfasts modulated blood levels of the amino acids tyrosine and tryptophan. Importantly, such modulations of blood level tyrosine and tryptophan predicted changes in participants' decision-making processes (Strang et al., 2017).

In contrast, observational methods require dietary assessment, which is vital for understanding how the dietary context affects brain function. For example, adherence to the Mediterranean diet was associated with larger cortical thickness in brain areas typically associated with age-related or neurodegenerative decline in cognitively normal elderly (Staubo et al., 2016). Table 1 provides an overview of dietary data collection methods with examples.

Table 1: Dietary data collection methods presented by Penn and colleagues (Penn et al., 2010).

Data collection methods	Examples
Self-assessments	Food records or diaries (with weighted intake or estimated weights, 24-hour recall, diet history (e.g., Food Frequency Questionnaire)
Digital imaging technologies	Technology-assisted dietary assessment using smartphone cameras (Zhu et al., 2008)
Bioinformatics and metabolomics	Biofluids (Blood, urine, saliva), doubly-labeled water[2]

[2] The doubly-labeled water method is the gold standard for measuring total daily energy expenditure in free-living individuals. After ingesting a dose of water enriched with the stable isotopes ^{2}H and ^{18}O, blood, saliva or urine is sampled. Differences in elimination rates of the two tracers combined with the respiratory quotient allows calculation of energy expenditure (Lifson et al., 1955).

Besides choosing a data collection method, dietary measures must be defined as outcomes or predictors. Table 2 lists different types of measures along with examples.

Table 2: Measures of dietary intake alongside examples (own representation: Muth).

Dietary intake	Examples
Nutrient intake	Carbohydrates, saturated fatty acids, zinc
Food item intake	Chips, bananas, walnuts
Food group intake	Fruit/vegetables
Indices of dietary quality	Dietary Inflammatory Index (Shivappa et al., 2014), Mediterranean Diet
Data-driven	Dietary patterns (Agnoli et al., 2019) using, e.g., Factor analysis or cluster analysis

1.4 Macronutrients

Macronutrients (carbohydrate, fat, protein) are the major dietary components supplying energy. Table 3 lists the three macronutrients, their simple forms, and examples of food that contain them. Essential macronutrients for the brain are glucose (Marty et al., 2007), amino acids (Fernstrom and Fernstrom, 2007), and fatty acids (Haag, 2002), thus warranting the study of macronutrients on cognitive performance.

Table 3: Macronutrients, their simple form, and food examples (own representation: Muth).

Macronutrient	Simple form	Examples of foods containing this nutrient
Carbohydrates	Simple (mono- and disaccharides)	Candy, cakes, cookies, ice cream, sugar-sweetened beverages
	Complex (starches and fiber)	Plant whole foods, broccoli, potatoes, barley, oatmeal, whole-wheat bread
Fatty acids	Saturated fatty acids (SFA)	Dairy, meat
	Monounsaturated fatty acids (MUFA)	Olive oil, nuts (e.g., almonds, cashews), avocados

	Polyunsaturated fatty acids (PUFA) includes omega-3 and omega-6	Avocados, peanuts, walnuts, olive oil, salmon
	Trans fats	Processed foods (e.g., frozen pizza, fried foods, refrigerated dough)
	Cholesterol	Meat, eggs, dairy
Proteins (digestion breaks proteins down into amino acids)	Plant-derived amino acids (incomplete proteins that do not contain all essential amino acids except soy)	Tofu, beans, lentils, chickpeas, almonds, quinoa, broccoli
	Animal-derived amino acids (contain all essential amino acids)	Eggs, meat, dairy, fish

1.5 Physical activity

Obesity and other lifestyle-related health problems are not only due to poor diets. A study using data from 1.9 million participants worldwide concluded that most people are not sufficiently active, posing a severe public health problem (Guthold et al., 2018). Adequate physical activity can multiply the benefits of a healthy diet and even counteract the negative consequences of poor dietary habits to some degree (Gomez-Pinilla, 2011; Vuori, 2001). For example, former athletes with high intakes of saturated fatty acids did not suffer impaired cognitive functions (Hinton et al., 2011). Moreover, physical activity increases wellbeing (Senaratne et al., 2021) and reduces the risk of experiencing a mental health disorder (Firth et al., 2020). These studies highlight the importance of considering physical activity alongside diet to assess their joint impact on mental health outcomes.

1.6 Research question

This doctoral thesis aimed to investigate how dietary intake impacts cognitive functioning and mental wellbeing. A better understanding of the specific factors of a healthy diet that affect brain functioning could guide interventions, health policies and motivate individuals

to make better dietary choices. Therefore, this work seeks to elucidate which dietary components affect cognition and mental wellbeing and propose a framework of the underlying mechanisms by which diet affects brain function.

1. Do dietary macronutrients affect cognitive performance and neural structures of the brain?

2. What are the mechanisms underlying the impact of macronutrient intake on cognitive performance and brain functioning?

3. Is dietary intake associated with mental wellbeing in a pandemic context when considering concurrent lifestyle factors?

To address these questions, a literature review was conducted (a) to assess how dietary macronutrients affect cognitive performance and brain structures and (b) to delineate the underlying mechanisms of such links.
Next, an online study was undertaken, capitalizing on the unique circumstances presented by the COVID-19 pandemic. This study investigated the links between food intake, lifestyle, and measures of wellbeing and mental health.

2 Methods

2.1 Literature search

The search and selection of relevant articles to answer question 1 were carried out following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) that guide transparent reporting of systematic reviews and meta-analyses. Covidence software (www.covidence.org) facilitated duplicate removal. Title, abstract and full-text screening were carried out in duplicate. Searches were conducted between August and September 2018. Table 4 presents search terms, databases, and inclusion criteria. We identified a total of 46 papers as suitable to address question 1. See Figure 1 for a flow diagram of the study selection process.

Table 4: Literature search parameters (own representation: Muth).

Electronic databases	Inclusion criteria
PubMed, Scopus	Peer-reviewed articles in English Publication date < 20 years ago
Search terms	Study population: healthy human adults
Macronutrient, cogniti*, carb*, glucose, protein, amino acid, fat, fatty acid, diet*, nutr*, food	Methodology: observational and experimental studies Measure: at least one macronutrient from whole-meal intake Outcome: at least one cognitive or brain measure

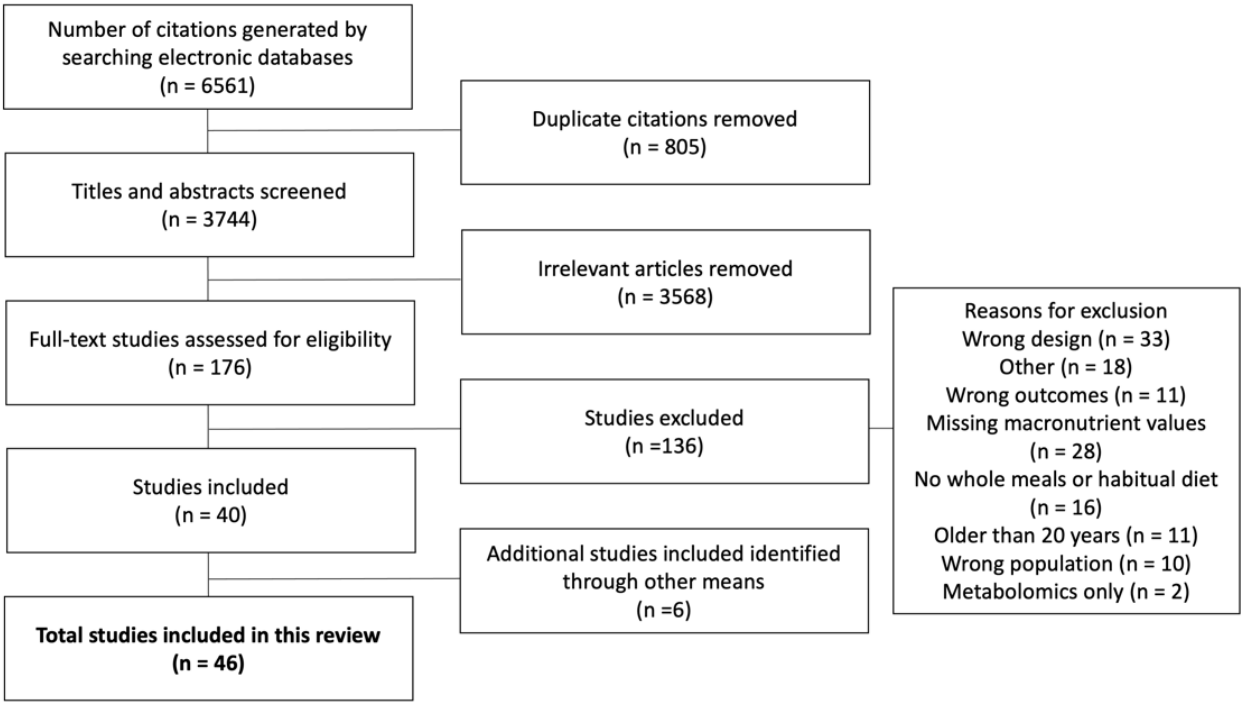


Figure 1: Flow diagram of the study selection process. Figure from Muth and Park (2021).

2.2 Participants and Design

In order to answer question 3, whether dietary intake is associated with mental wellbeing we conducted an observational study online, capitalizing on the unique circumstances presented by the COVID-19 pandemic during a light lockdown[3] in Germany in November 2020. The sample size was determined using G*Power (Faul et al., 2007) a priori for multiple linear regression with a small effect size Cohens f = .15 and alpha = .05 assuming three tested predictors and six total predictors and a power estimated at .95, recommending a sample of N = 119.

Recruitment was done via the online platform Prolific (www.prolific.co). See Table 3 for eligibility criteria. When entering the platform, participants were informed about the study and asked for their consent. The ethics commission of the Humboldt University of Berlin approved this study.

Table 5: Eligibility criteria (own representation: Muth).

Inclusion criteria	Exclusion criteria

[3] During this lockdown people were asked to reduce social contacts to the necessary minimum. In public, a maximum of two households could meet.

German-speakers residing in Germany at the time of study	Prior or current mental health diagnosis
Age 18 and above	Severe score (< 30) on depression questionnaire
Android or Apple Smartphone	Fewer than three diary entries

An overview of the study design is shown in Figure 2. Participants completed mental health and wellbeing baseline and trait questionnaires at the beginning of the study (findings on these are reported elsewhere, (Vermeer et al., 2022). They were then asked to keep a diary of their food intake, mood ratings, and behavior ratings for seven days using the FoodApp. Using the Food App allowed us to make ecological momentary assessments, thereby capturing food intake and ratings of mood and behavior as they happened. At the same time, the participant could not see previous entries, thus minimizing their influence on behavior.

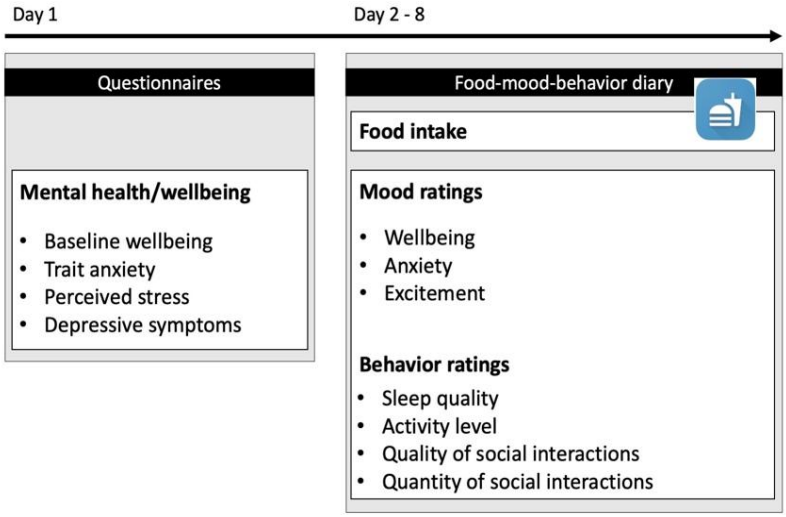
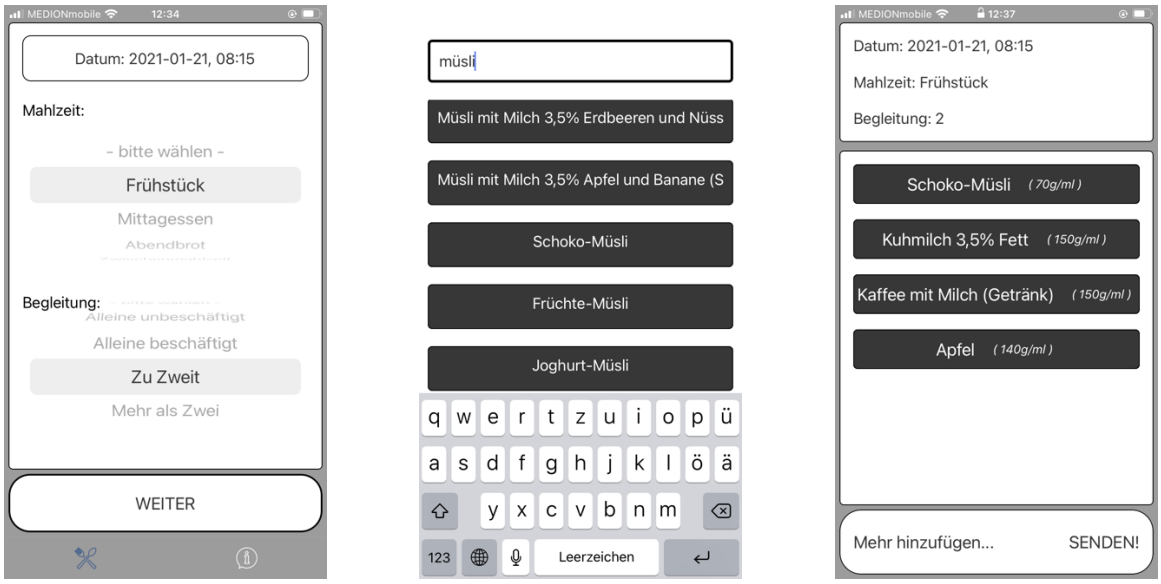


Figure 2: Online study design (modified from Muth et al. 2022).

Participants searched for the food items they wanted to submit to the food diary using the search box in the FoodApp (see Figure 4). Participants also provided information on meal time and type and whether they ate in company or alone. The food items in the food diary came from the German Federal Food Key Data table (Dehne et al., 1997). This food key allowed extraction of the nutrient content of each food item, meal, and day for each participant. In particular, we were interested in carbohydrate, fat, and fruit/vegetable intake. Additionally, we computed the dietary inflammatory index score (Shivappa et al., 2014;

see Muth et al., 2022 for details) for each person because the previously conducted literature review (Muth and Park, 2021) found that inflammation is a major pathway between dietary intake and brain functioning.



(a) (b) (c)

Figure 3: Screenshots of the FoodApp. (a) Participants were asked to provide information about the time of the meal, the type of meal, and whether they ate alone or in company. (b) Shows the food item search box and the choice of food items they can log. (c) Shows the chosen food items corresponding to a breakfast eating in the company of another person (own representation: Muth).

Once per day in the evening, the FoodApp displayed questions to assess daily mood and lifestyle behavior (see Figure 4). Daily mood was captured by assessing wellbeing, emphasizing functional aspects using the 7-item short version of the Warwick-Edinburgh Mental Wellbeing Scale (Tennant et al., 2007). It includes questions such as "I've been thinking clearly" and "I've been feeling optimistic about the future" that are answered on a 5-point Likert scale with a total score ranging from 7 to 35. According to the analysis guidelines, scores between 7 and 17 may signify probable depression and anxiety, and scores between 18 and 20 suggest possible depression.

We complemented the short mental wellbeing scale with an additional question about anxiety and excitement (also on a 5-point Likert scale, taken from the Positive Affect Negative Affect Scale (Breyer and Bluemke, 2020; Watson et al., 1988). Daily behavior ratings

included questions about sleep quality, physical activity level, social interaction quality and quantity rated on a scale from 1 to 100.

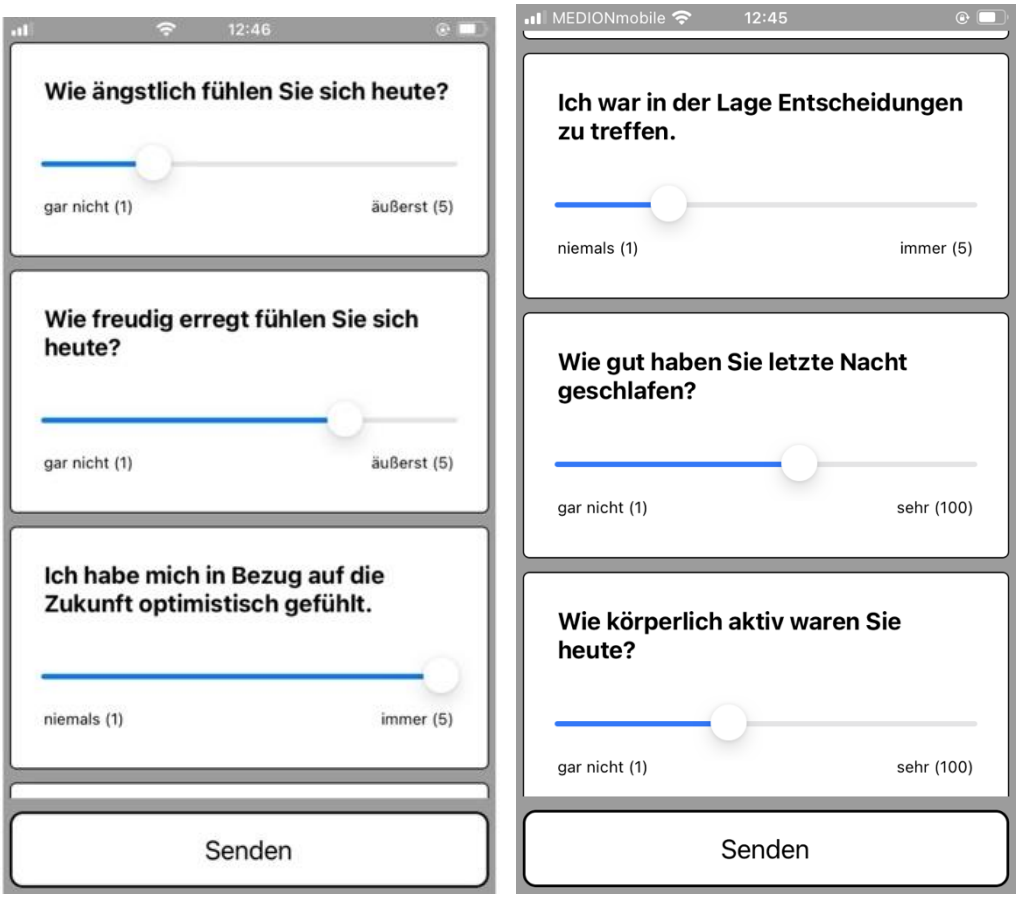


Figure 4: Screenshots of the FoodApp. (a) Shows questions about anxiety, feeling excited and mental wellbeing. (b) Shows rating scales regarding sleep quality and level of physical activity (own representation: Muth).

2.3 Statistical analyses

Questionnaire data, FoodApp data, and demographic data were downloaded and loaded into RStudio (Team, 2021). The tidyverse package (Wickham et al., 2019) facilitated data wrangling (e.g., removing duplicate responses, matching participant IDs, and joining data files). Dietary data were winsorized[4] separately for each gender by using the DescTools

[4] Winsorizing reduces the influence of outliers by reassigning extreme values to a percentage of cases, thereby creating more robust estimators (Frey, 2018).

package (Signorell, 2021) to the 5%-quantile for minimum values and 95%-quantile for maximum values.

We calculated weekly averages of the daily diary entries for between-subject analyses and conducted three separate analyses for each averaged dependent variable (DV): well-being, anxiety, and excitement. The multiple linear regression models were specified as follows (Muth et al., 2022)[5]:

DV ~ fruit/vegetable + fat + carbohydrate + physical activity + sleep + quality of social interaction + quantity of social interaction + male gender

Mediation analyses were performed using the MeMoBootR package (Buchanan, 2021) to test whether any of the lifestyle factors mediated an effect of food intake on wellbeing when controlling for all other lifestyle factors.

Daily food, mood, and lifestyle entries were entered into within-subject analyses using mixed-effect models. We tested the temporal effects of lagged food intake (up to two days back in time) on wellbeing after controlling for daily lifestyle factors and the previous day's wellbeing. Likewise, we tested whether lagged food intake and lifestyle (i.e., sleep, physical activity, and social interactions) predicted self-rated anxiety or excitement (see equations 2-4 in Muth et al., 2022).

Gender differences were explored by marginal means analysis using the emmeans package (Lenth, 2021) and visualized with sjPlot (Lüdecke, 2021). We used the ggstatsplot package (Patil, 2021) for all other plots.

[5] Note that the power calculation was calculated for 6 total predictors, however we made some changes to the predictors we included, such as adding gender. A detailed description of which changes we made to the preregistration can be found in the manuscript (Muth et al., 2022).

3 Results

3.1 Literature review

The narrative literature review synthesized the evidence on whether (a) carbohydrates, fats, and proteins from whole meals impact cognitive functioning and the brain in healthy adults, and (b) elucidated underlying mechanisms that link macronutrient intake and effects on brain and cognition.

The types of carbohydrates and fatty acids matter: high intakes of simple carbohydrates, saturated fatty acids, and trans fats were associated with impaired cognitive functioning (Muth and Park, 2021). In contrast, consumption of complex carbohydrates and polyunsaturated fatty acids is generally related to improved cognitive performance (Muth and Park, 2021). Findings are less clear for monounsaturated fatty acids and dietary cholesterol (Muth and Park, 2021). For protein intake, the literature clearly distinguished between short-term and long-term effects (Muth and Park, 2021). When task demands are high, or stressors are present, acute dietary protein can uphold task performance in tasks probing memory and cognitive control (Muth and Park, 2021). In advanced age, adequate intake levels become essential and are associated with maintained levels of global cognitive functioning, whereas both over- and under-consumption correlate with poor working memory (Muth and Park, 2021). Table 6 presents an overview of findings by macronutrient type and cognitive function.

Table 6: The effects of macronutrients on cognitive function (modified from Muth and Park, 2021).

Macronutrient		Cognitive function
Carbohydrates	Simple	↓ Global cognitive function[6]
	Fiber	↑ Memory, ↓ cognitive decline
Fatty acids	Saturated fatty acids	↓ Memory, learning
	Monounsaturated fatty acids	↑ ↓ Memory, risk for mild cognitive impairment

[6] Global cognitive function refers to performance assessed by cognitive test batteries that assess multiple cognitive functions.

			↑ Global
	Polyunsaturated fatty acids		↑ Memory, psychomotor processing
	Trans fats		↓ Memory, learning ↓ Cognitive decline
	Cholesterol		↑ ↓ Global cognitive function ↓ Learning
Protein (animal or plant-based)	Short-term (acute meal)		↑ Inhibition, reaction time
	Long-term (habitual diet)	optimal intake	↑ Fluid intelligence, memory, working memory, global cognitive function
		too much/too little	↓ Working memory ↑ Risk for mild cognitive impairment

↑ improved/faster/increases in, ↓ decreases in or diminished function, ↑↓ mixed findings

From the above literature, several mechanisms emerged: glucose and insulin metabolism, neurotransmitter actions, oxidative and inflammatory processes, as well as the influence of the gut-brain axis. These mechanisms link dietary macronutrient intake and cognitive function. However, an overarching framework was still missing in the literature. Here, I examined central mechanisms and provided a framework highlighting the interrelationships between mechanisms (Figure 5).

3.2 Glucose and insulin metabolism

The brain requires glucose to function, making glucose and insulin metabolism the most prominent pathway linking macronutrient intake to cognitive functioning (Muth and Park, 2021). Glucose and insulin can cross the blood-brain barrier via specialized transporters, such as GLUT1 for glucose (Bell et al., 1990). Habitual consumption of a high-fat diet is linked to reduced expression of GLUT1, which leads to impaired spatial memory function in mice (Jais et al., 2016).

3.3 Neurotransmitters

How do macronutrients affect neurotransmitter actions in the brain? Digestion breaks proteins down into amino acids. Some of these amino acids are the building blocks (precursors) of neurotransmitters. For example, tryptophan and tyrosine are two large neutral amino acids that are precursors of serotonin and dopamine (amongst others), respectively (Fernstrom, 2012). To be synthesized into brain neurotransmitters, these amino acids need to cross the blood-brain barrier. However, tryptophan and tyrosine, the dopamine precursor, compete for transport through the blood-brain barrier (Fernstrom and Wurtman, 1971). Tryptophan additionally requires insulin to cross the blood-brain barrier. Thus, the ratio of carbohydrates to protein of a meal influences which of these precursors preferentially gets carried across. A meal rich in carbohydrates increases blood tryptophan levels, whereas a protein-rich meal increases blood levels of tyrosine (Choi et al., 2009; Wurtman et al., 2003).

Once these precursors are synthesized into neurotransmitters in the brain, they affect multiple actions in the brain by transmitting messages between neurons (Webster, 2001). For example, neurotransmitters control vigilance, action, reward learning, and memory (Ranjbar-Slamloo and Fazlali, 2020).

3.4 Brain oxidation and inflammation

A prolonged diet high in sugar and saturated fatty acids can lead to insulin resistance, a hallmark of impaired insulin metabolism (Deer et al., 2014). Insulin resistance fosters oxidation and inflammation in the brain (Rains and Jain, 2011). Oxidation – the release of reactive oxygen species as a by-product of mitochondrial metabolism – is tolerable in low levels (Lehninger et al., 1958). However, excessive Reactive oxygen species levels that fail to be neutralized by antioxidants cause oxidative stress to the brain (Salim, 2016). A poor diet can induce chronic low-level inflammation in the brain, which sustains insulin and leptin resistance, thereby entering a vicious cycle whereby poor insulin metabolism promotes inflammation, which promotes insulin resistance (Dantzer et al., 2008; Lasselin et al., 2016). These processes are linked to dementia, depression, mild cognitive impairment, and structural brain changes, evident in decreased cortical thickness, loss of grey matter, and vascular damage (Akintola et al., 2015; Grande et al., 2020; Pugazhenthi et al., 2017).

3.5 Gut-brain axis

The large intestine ferments dietary fiber to short-chain fatty acids (Flint et al., 2012), which have multiple purposes in the body. Short-chain fatty acids supply energy, help maintain glucose levels and protect the integrity of the blood-brain barrier (Bienenstock et al., 2015; Mohajeri et al., 2018). The integrity of the blood-brain barrier is essential because it protects against neuroinflammation (Sampson and Mazmanian, 2015). In addition, a high-fat diet undermines beneficial bacteria while fostering Firmicutes, which are also associated with neuroinflammation (Proctor et al., 2016). In mouse models, this led to anxious behavior (Desbonnet et al., 2015). Most of the existing literature is currently limited to mouse models, awaiting translation to the human population (Muth and Park, 2021).

3.6 A framework of major pathways linking macronutrient intake and brain function

In sum, multiple pathways exist that plausibly link macronutrient intake and brain function together (see Figure 5 modified from Muth and Park, 2021; or Figure 2 in Muth and Park, 2021). Acute pathways are via glucose and insulin metabolism, which also affect neurotransmitters. A disturbed glucose metabolism can lead to long-term alterations that affect brain oxidation and inflammation to the extent that may impact brain structures. Finally, the gut-brain axis affects both glucose and insulin metabolism and neuroinflammation.

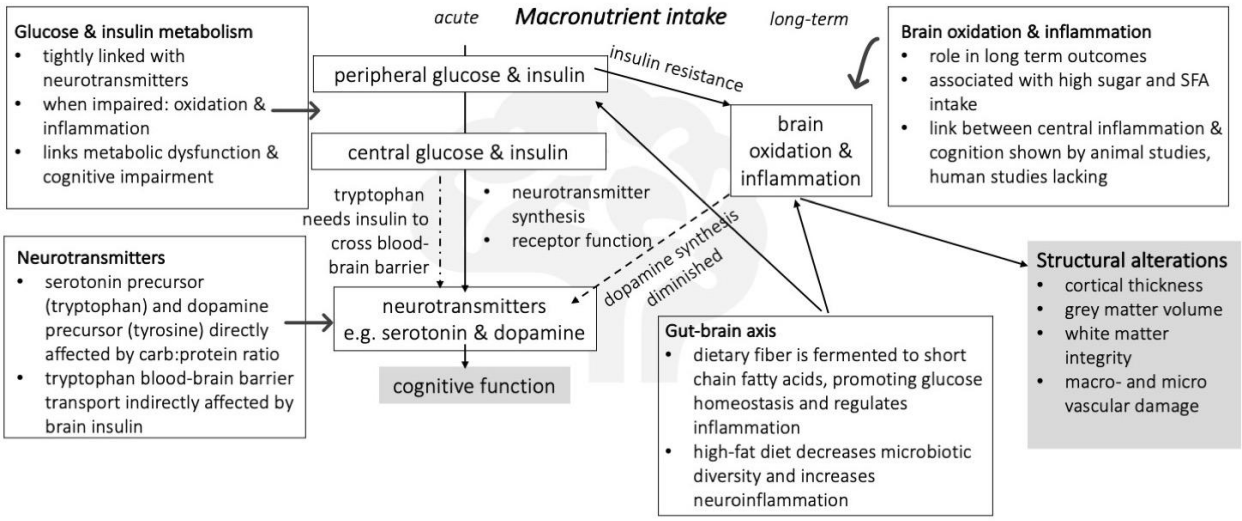


Figure 5: A framework of the multiple pathways that link macronutrient intake, brain function and structure. SFA: saturated fatty acids (modified from Muth and Park, 2021).

3.7 Descriptive statistics

A total of 117 participants completed baseline questionnaires on mental health and well-being and a seven-day food-mood-behavior diary during light lockdown in November 2020 in Germany. Participants logged between 1 and 12 days of food intake (M = 8d) and between 1 and 9 days of mood and lifestyle diary entries (M = 6.4d). However, we removed data from participants who entered fewer than three diary entries and more than 8 (N = 15). Demographic participant characteristics, average food intake, and mood scores are summarized below in Table 7. For more detail, see Table 1 (Muth et al., 2022).

Table 7: Sample characteristics (modified from Muth et al., 2022).

	Total (N = 117)[1]	Women (n = 45)[1]	Men (n = 72)[1]	p-value[2]
Age	28.12 (8.91)	30.76 (10.44)	26.47 (7.42)	0.009
BMI	24.21 (4.18)	23.50 (4.27)	24.65 (4.09)	0.016
Daily averaged food intake				
Kilocalories	1,727.09 (504.04)	1,513.31 (437.25)	1,860.71 (499.53)	<0.001
Protein % of kcal	16.44 (4.26)	15.27 (2.62)	17.17 (4.89)	0.020
Carbohydrate % of kcal	47.85 (6.79)	48.49 (7.20)	47.44 (6.54)	0.4
Fat % of kcal	34.47 (6.59)	34.81 (7.90)	34.25 (5.67)	0.8
Fruit/vegetable (g/1000kcal)	73.82 (43.70)	91.96 (35.17)	62.48 (44.89)	0.009
Dietary Inflammatory Score	0.00 (1.92)	0.15 (1.86)	-0.09 (1.97)	0.6
Daily averaged mood scores				
Wellbeing	22.26 (2.84)	22.11 (3.01)	22.35 (2.75)	>0.9
Excitement	3.07 (0.64)	3.01 (0.74)	3.10 (0.56)	0.6
Anxiety	1.88 (0.66)	2.10 (0.65)	1.74 (0.64)	0.003

[1] Mean (SD); n (%)

[2] Wilcoxon rank-sum test; Pearson’s Chi-squared test; Fisher’s exact test

3.8 Fruit/vegetable intake predicts wellbeing between-subjects

Between-subject wellbeing (i.e. averaged over the week) was predicted by fruit/vegetable intake (B = 0.01, p = .013), sleep quality (B = 0.05, p < .001), social interaction quality (B = 0.10, p < .001) and male gender (B = 0.86, p = .048), see Figure 6 for a visualization of coefficient estimates.

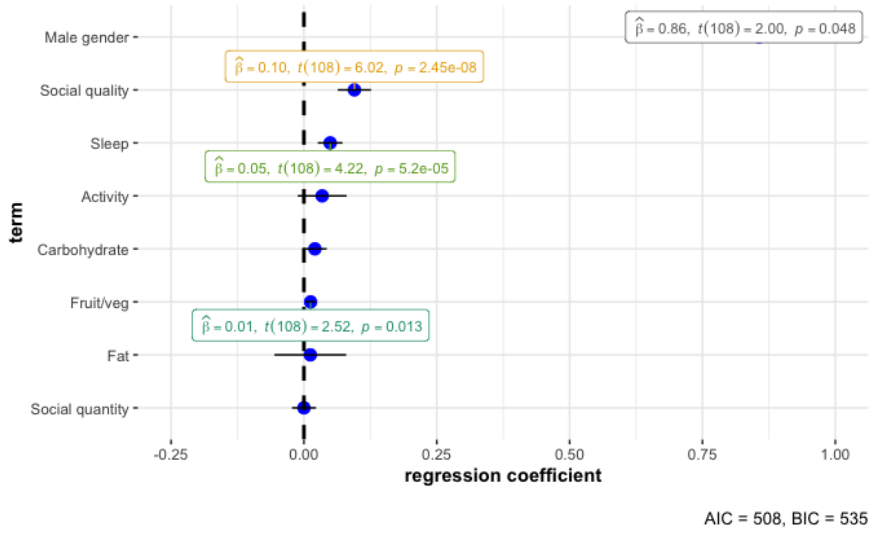
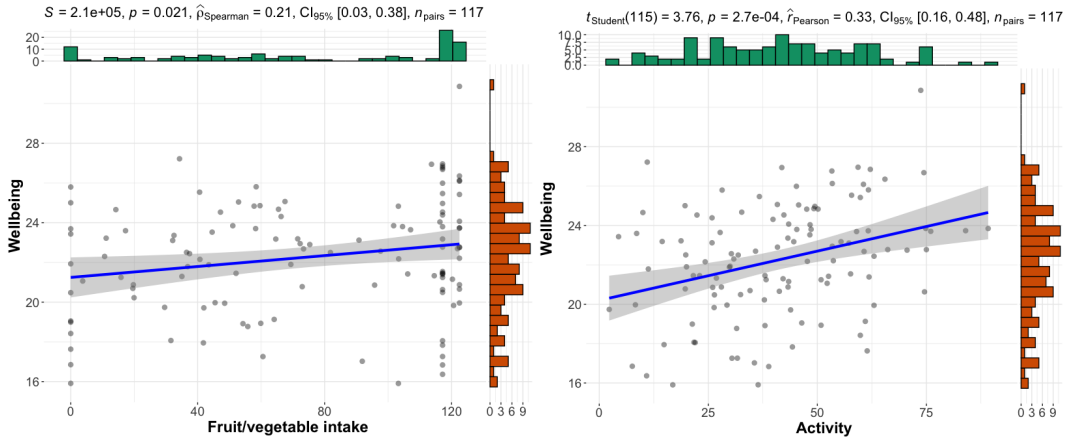


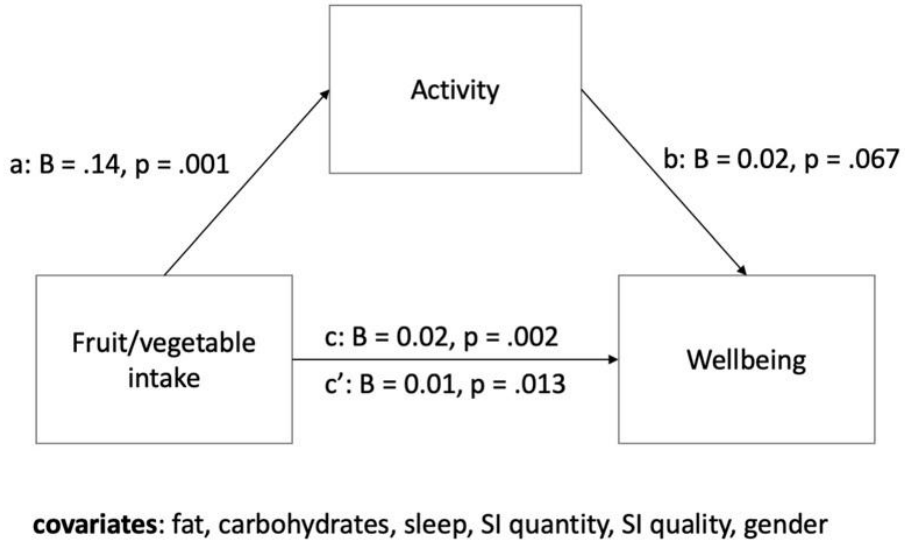
Figure 6: Between-subject regression coefficients for predicting wellbeing. Intercept (B = 6.48, p = 0.093) not shown here. Non-standardized regression coefficients are shown. Statistics are shown only for significant regressors (own representation: Muth).

3.9 Physical activity partially mediates the effect of fruit/vegetable intake on well-being between-subjects

All dietary components (carbohydrates, fat, fruit/vegetable intake) were tested to see if any of them regressed onto wellbeing. Only fruit/vegetable intake did (B = 0.02, SE = 0, t = 3.20, p = .002). Then, we tested whether fruit/vegetable intake regressed on any life-style factors (sleep, physical activity and social interaction quality). Only physical activity could be predicted by fruit/vegetable intake (B = 0.14, SE = 0.04, t = 3.35, p = .001). Therefore, we ran only this one mediation model, which confirmed that physical activity partially mediated the direct effect of fruit/vegetable intake on wellbeing (direct effect: B = 0.01, p = .013; total effect: B = 0.02, p = .002; bootstrapped indirect effect (ab): B = 0.03, SE = 0, 95% CI -0.00 – 0.01). For a visualization see Figure 7.



(a) (b)



(c)

Figure 7: Physical activity partially mediates the effect of fruit/vegetable intake on wellbeing. Panel (a) shows the correlation between fruit/ vegetable intake and wellbeing; (b) shows the correlation between self-rated physical activity and wellbeing, and (c) shows the mediation model. Figures (a) and (c) from Muth et al. (2022).

3.10 Same day fruit/vegetable intake predicts wellbeing within-subjects

Mixed effect models allowed testing within-subject changes in wellbeing levels (i.e., day-to-day changes). Same-day fruit/vegetable intake predicted wellbeing (B = 0.01, p = .002), but neither next-day (B = -0.00, p = .301) or day-after-next level of wellbeing (B = -0.00,

p = .253). All lifestyle factors (sleep quality, physical activity level, social interaction quality and quantity) significantly predicted same-day wellbeing. Lifestyle factors were entered as covariates, and therefore temporal effects were not tested for sleep, physical activity, or social interactions. In sum, as predicted, fruit/vegetable intake predicted wellbeing in between- and within-subject analyses.

3.11 Food intake did not predict anxiety or excitement

In contrast to wellbeing, fruit/vegetable intake did not predict anxiety or excitement between-subjects (see Table 2 in Muth et al., 2022) or within-subjects on the same day, one day later, or two days later (Tables 3, 5, and 6 in Muth et al., 2022, respectively). Similarly, carbohydrate and fat intake did not predict wellbeing, anxiety, or excitement between-subjects (see Table 2 in Muth et al., 2022) or within-subjects (Tables 3, 5, and 6 in Muth et al., 2022, respectively).

3.12 Dietary Inflammatory Index is associated with wellbeing and mediated by physical activity

The literature review examined the role of inflammation as a mechanism by which diet affects brain functioning. Therefore, I investigated if a high dietary inflammatory index correlated with lower wellbeing[7]. Indeed, dietary inflammatory index correlated negatively with average wellbeing (r = -0.20, p = .027) but neither with anxiety (r = 0.17, p = .063) nor excitement (r = -0.09, p = .332). Similarly, to the mediation analysis above with the between-subject comparison, we found that physical activity fully mediated the direct effect of dietary inflammatory index score in wellbeing (direct effect: B = -0.14, p = .191 total effect: B = -0.21, p = .047; bootstrapped indirect effect: B = -0.07, SE = 0.04, 95% CI -0.15 - 0.00).

[7] Please note that this hypothesis was not preregistered and was carried out exploratively.

4 Discussion

4.1 Short summary of results

This doctoral thesis investigated whether and how dietary components affect cognitive functioning and mental wellbeing, and proposed a framework of underlying mechanisms. Thus, this work provides three key results that address the research questions posed in the introductory chapter.

1. The narrative review synthesized existing literature and contributes to the field of nutritional neuroscience by providing the initial overview of how the macronutrient intake from whole meals impacts on cognitive function and the brain. It was found that macronutrient intake has both short- and long-term effects on the brain and cognitive functioning. In short, the types of carbohydrates and fatty acids played a role in whether effects on brain function where positive or negative, while for protein the adequate intake was important, especially under high task demands and for elderly populations.

2. A novel framework was proposed that describes four key mechanisms by which food intake acts on the brain and cognition. These mechanisms are glucose and insulin metabolism, neurotransmitters, brain oxidation and inflammation and finally, the gut-brain axis.

3. Data collected via an online study during a pandemic lockdown confirmed that certain dietary intake, namely fruit and vegetable intake, played positively affected psychological wellbeing while taking concurrent lifestyle factors into consideration.

In sum, this work confirms the role that dietary intake plays for cognitive functioning, wellbeing and the brain, with respect to dietary macronutrient and fruit and vegetable intake.

4.2 Interpretation of results

The literature search provided evidence that a diet characterized by a balanced macronutrient intake, with plenty of fruit, vegetables, legumes, and whole grains, as well as high-quality seafood and vegetable oils, supports healthy brain function throughout life

(Muth and Park, 2021). In line with these findings, studies focusing on neurodegenerative diseases find that certain macronutrients are consistently associated with an increased risk (such as high intake of saturated fats and simple carbohydrates) and others with decreased risk (polyunsaturated fatty acids for example; Baranowski et al., 2020). Similarly, nutrients like omega-3 fatty acids, are associated with anti-inflammatory actions and act neuroprotectively (McGrattan et al., 2019).

The findings of the online study largely align with previous studies conducted before the pandemic (Blanchflower et al., 2013; Mujcic and J.Oswald, 2016; Ocean et al., 2019; White et al., 2013) and during the COVID-19 pandemic (Hu et al., 2020). However, the positive effect of fruit/ vegetable intake on wellbeing did not extend to anxiety. Correspondingly, a recent meta-analysis found that only fruit intake lowered the risk of anxiety symptoms; neither vegetable nor fruit/vegetable intake together showed ameliorating effects on anxiety (Liu et al., 2020). Similarly, fruit/vegetable intake did not predict excitement (as a measure of positive affect) even though earlier studies found a mood-boosting effect of fruit/vegetable intake (Ford et al., 2020; Warner et al., 2017; White et al., 2013).
Contrary to the preregistered hypotheses, neither fat nor carbohydrate intake predicted wellbeing, anxiety, or excitement on a daily or weekly level. This is in contrast to previous findings reporting that food preferences in times of stress shift towards higher carbohydrate and fat intake (Roberts et al., 2013), which corresponds with more negative mood (Epel et al., 2001). Maybe the overall decline in dietary quality during lockdown (Marty et al., 2021) towards comfort eating to cope with the stressful situation (Bemanian et al., 2021; Renzo et al., 2020) masked these effects. Alternatively, it may be that other lifestyle behaviors during lockdown undermined the impact of diet on wellbeing and mood, such as physical activity and social interactions (Muth et al., 2022). Indeed, social interactions negatively predicted anxiety, showing that this may have become more important in times of social distancing. Similarly, daily excitement was also predicted by social interaction, sleep quality, and physical activity level.
We also tested whether an inflammatory diet affected wellbeing. Only one study has previously investigated the relationship between an inflammatory diet and wellbeing using a dedicated wellbeing questionnaire (Phillips et al., 2018). In line with our findings, an inflammatory diet was associated with lower wellbeing. However, while we found that physical activity mediated this relationship, Philipps and colleagues did not find an effect of

physical activity (Phillips et al., 2018). It may be that the specific circumstances of lockdown enhanced the importance of physical activity (Muth et al., 2022). In support, highly active people before lockdown experienced greater wellbeing declines than inactive individuals (Martínez-de-Quel et al., 2021).

4.3 Embedding the results into the current state of research

Previous work often focused on nutrition in relation to development or neurodegenerative disease; such as school children, frail elderly, or people suffering from Alzheimer's disease. Such studies have typically considered the effects of malnutrition on cognitive function (Morris 2012, Tucker 2016) or whether nutrients are associated with biomarkers of neurodegeneration (Kalli 2017). Even fewer studies examined how nutrition affects cognitive function in healthy people and of those studies, most addressed micronutrients, such as vitamins and minerals. Here, this gap was filled by examining the impact of macronutrients in healthy adults with regards to cognitive performance and brain structures.

In addition, a novel framework was postulated, that considers how the underlying mechanisms act together. Previously suggested frameworks have considered specific aspects, such as the microbiome and how it affects the gut-brain axis (Ezra-Nevo et al., 2020) or how a plant-based diet affects behavior and cognition (Medawar et al., 2019). In contrast, the framework presented here attempts to get a broader view than previous work. This is an important step, as it both deepens our understanding of how diet affects cognition but also allows testing hypotheses that are high in ecological validity.

Finally, we focused on a specific aspect of dietary intake and whether it plays a role mental wellbeing while considering contextual lifestyle factors. Previous work had considered the effects of specific nutrients or dietary styles on mood and mental health (e.g. Głąbska et al., 2020, Psaltopoulou et al., 2013, Sánchez-Villegas et al., 2011) but often neglected other behaviors that co-exist and are well-known to affect both mood and mental health. The present work extends previous work by showing the impact of diet on wellbeing while taking concurrent lifestyle factors into account. In addition, this study complements previous research findings conducted during the pandemic. For instance, one study showed that lower dietary quality correlated with negative mood (Marty et al., 2021), while we

could show that this relationship can also work the other way around; with increased fruit and vegetable intake showing more wellbeing.
In sum, the present work further contributes to our understanding of the effects of diet on cognition and wellbeing while considering the biopsychosocial context more closely.

4.4 Strengths and weaknesses of the studies

The literature study used a systematic search, following the PRISMA guidelines (Page et al., 2021), ensuring a wide and thorough search of the available literature. However, a systematic review was not conducted. This was mainly due to the fact that a major challenge in the study of nutrition, cognition, and the brain is that the methodologies between studies differ widely (Galioto and Spitznagel, 2016; Muth and Park, 2021; Teo et al., 2017). Often, they lack the necessary detail of the foods tested (Dye et al., 2000) or select inadequate tasks that may not be sensitive enough (Dye et al., 2000; Macready et al., 2010). Thereby, not allowing for the rigorous scrutiny that would be desirable.

The design of the online study resulted in a rich data set using ecological momentary assessments (Schembre et al., 2018) of dietary intake, wellbeing measures, and concurrent lifestyle ratings. Capturing daily food intake via a smartphone app has several advantages over other methods, such as 24-hour recall or paper-pencil diary methods (Schembre et al., 2018). Firstly, participants can submit their intake right away, which prevents omissions due to forgetting when recording is delayed. Once submitted, participants cannot see previous entries, limiting potential biases and dangers resulting from tracking behaviors (Simpson and Mazzeo, 2017). Secondly, integration with the German food composition database (Dehne et al., 1997) allowed precise and automated calculation of nutrient content. The mood-lifestyle measures further allowed us to investigate day-to-day changes within individuals, which enabled us to test relationships that had not been investigated previously, such as whether concurrent social interactions affected wellbeing in addition to dietary intake. For example, we controlled for social interaction quality, which was particularly relevant during lockdown because social distancing measures have resulted in increased rates of depression and anxiety in Germany (Benke et al., 2020). Finally, a strength is that we preregistered our analysis plan and hypothesis ahead of data collection.

Limitations include that we did not ask participants to weigh their foods. Weighted records are currently considered the gold standard of dietary self-reports (Penn et al., 2010). The dietary data underlies self-reporting biases, and caloric intake is likely underreported, as evident by the low total caloric intake shown in Table 7 (Muth et al., 2022). However, we did not ask participants to, to increase the compliancy. Secondly, different dietary outcome measures may have led to other findings. For example, using factor analysis to assess dietary patterns may have informed which dietary patterns are associated with wellbeing. Finally, we collected data during a lockdown period, meaning we do not have data from before, so we cannot compare whether people's behavior changed. Likewise, we cannot conclude whether our findings generalize to a time outside of lockdown (e.g., whether physical activity mediates the effect of fruit/vegetable intake on wellbeing when there are no pandemic-related restrictions).

4.5 Implications for practice and/or future research

The study of nutrition would be improved by (1) careful consideration of the methods by which dietary intake is assessed, allowing for examination of the complex dynamics between nutrients on metabolism and brain function, and (2) the selection of tasks that are sufficiently sensitive to detect changes based on the existing literature.

Clinicians could apply the knowledge of dietary effects on brain functioning and wellbeing to interventions aimed at preventing cognitive impairment in an aging population. A better understanding of lifestyle factors has overtaken the earlier predominant view that low functioning was inherent to the aging process (Rowe and Kahn, 1997). For instance, a review of dietary patterns and successful aging found a positive link between healthy dietary patterns and favorable health outcomes in older adults, such as reduced risk of premature cognitive decline (Milte and McNaughton, 2016).

We designed a follow-up project to investigate dynamics between habitual lifestyle (including dietary intake) and cognitive performance which depends on acute nutrition metabolism. This project combines observation methods to capture habitual lifestyle correlates (such as dietary intake and physical activity) with an experimental part consisting of two test days separated by a washout phase (Figure 12). Height, weight, and body composition are measured on each test day, followed by blood samples, (functional) magnetic resonance imaging, cognitive tests, and questionnaires. Importantly, participants eat a

test meal on each day (randomized, counter-balanced and administered blindly). Test meals resemble standard German breakfasts. Meal A is rich in carbohydrates, while Meal B is rich in proteins with the same fat percentage. The presentation of test meals is blinded and randomized across participants.

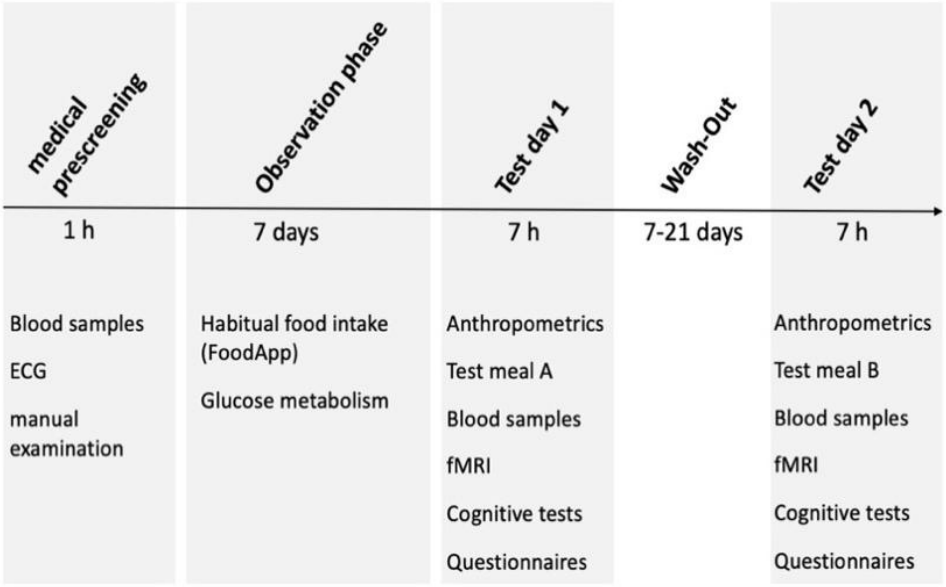


Figure 8: Proposed study design for a follow-up study to investigate the impact of nutrition and lifestyle on metabolism and brain function (own representation: Muth).

The resulting data set will allow testing many hypotheses regarding diet, lifestyle, metabolic, cognitive performance, and brain function. Based on prior findings (Strang et al. 2017), we expect elevated plasma tryptophan levels following the carbohydrate-rich breakfast and elevated plasma tyrosine levels following the protein-rich breakfast. To better understand the role of habitual diet in glucose and amino acid metabolism, one could test whether the habitual diet's carbohydrate to protein ratio predicts the area under the curve of acute tyrosine levels following the protein-rich meal and tryptophan following the carbohydrate-rich breakfast. Similarly, it would be interesting to see whether the average glucose response after meal intake predicts the area under the curve for tryptophan following the carbohydrate-rich meal.

Furthermore, testing whether cognitive performance is affected following an experimental meal and whether it depends on dietary habits could contribute to our understanding of the relationship between diet and cognition. Finally, recent studies have investigated the effects of physical activity on dopamine metabolism using mouse models of

Parkinson's disease (e.g., Iggena et al., 2019) and obesity (e.g., Totten et al., 2021). An interesting question would be whether an active lifestyle affects tyrosine plasma levels following the protein-rich meal and whether this affects cognitive performance sensitive to dopamine, such as reinforcement learning tasks (Dabney et al., 2020).

5 Conclusions

Together this work confirms that dietary components play a decisive role in affecting cognitive outcomes and mental wellbeing. Furthermore, the proposed framework maps out the mechanisms underlying the relationship between dietary macronutrients and brain functioning. The findings presented here also highlighted the importance of jointly considering concurrent lifestyle factors to evaluate the impact of diet in a meaningful context.

In conclusion, the link between diet, lifestyle, and brain function has important implications for future clinical practice and public health. The newly emerging field of nutritional psychiatry will benefit from understanding the mechanisms so that potential novel treatments can be designed for vulnerable populations at risk for mental health and poor brain aging. In the future, diet and lifestyle interventions may perhaps replace pharmacological interventions. Thereby, these studies contribute to the research on the intersection of nutrition, psychology, psychiatry, and neuroscience.

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Statutory Declaration

“I, Anne-Katrin Muth, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “The effects of dietary intake on cognitive functioning, wellbeing, and the brain" (in German: Die Auswirkungen der Ernährung auf kognitive Funktionen, Wohlbefinden und das Gehirn), independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; http://www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Declaration of your own contribution to the publications

Anne-Katrin Muth contributed the following to the below listed publications:

Publication 1: Muth AK & Park SQ, The impact of dietary macronutrient intake on cognitive function and the brain, Clinical Nutrition, 2021
Contribution (please set out in detail):

- Conceptualization, formulation of research question
- Data collection, data analysis and interpretation
- Writing – original draft preparation, visualization (all tables, all figures), revision

Publication 2: Muth AK, Losecaat Vermeer A, Terenzi D, Park SQ. The impact of diet and lifestyle on well-being in adults during COVID-19 lockdown. Frontiers in Nutrition, 2022
Contribution (please set out in detail):

- Conceptualization, project administration (together with Park SQ)
- Investigation, visualization and writing – original draft preparation
- Methodology and formal analysis (together with Losecaat Vermeer A and Park SQ)
- Writing – review and editing (together with Losecaat Vermeer A, Terenzi D and Park SQ)

_____

Signature, date and stamp of first supervising university professor / lecturer

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Signature of doctoral candidate

Excerpt from Journal Summary List

Publication 1:

Muth AK, Park SQ. The impact of dietary macronutrient intake on cognitive function and the brain. Clin Nutr. 2021 Jun;40(6):3999-4010. doi: 10.1016/j.clnu.2021.04.043. Epub 2021 May 1. PMID: 34139473.

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI
Selected Categories: **"NUTRITION and DIETETICS"** Selected Category Scheme: WoS
Gesamtanzahl: 89 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	PROGRESS IN LIPID RESEARCH	6,139	15.083	0.005730
2	Annual Review of Nutrition	5,766	10.897	0.005060
3	CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION	15,322	7.862	0.017050
4	NUTRITION RESEARCH REVIEWS	2,623	7.641	0.002190
5	Advances in Nutrition	6,142	7.265	0.011780
6	AMERICAN JOURNAL OF CLINICAL NUTRITION	59,398	6.766	0.045330
7	International Journal of Behavioral Nutrition and Physical Activity	11,154	6.714	0.018870
8	NUTRITION REVIEWS	8,817	6.500	0.008580
9	CLINICAL NUTRITION	15,002	6.360	0.019390
10	FOOD CHEMISTRY	122,430	6.306	0.108660
11	PROCEEDINGS OF THE NUTRITION SOCIETY	5,906	5.577	0.005350
12	Hepatobiliary Surgery and Nutrition	939	5.296	0.002520
13	Current Obesity Reports	1,463	5.259	0.004560
14	Journal of the International Society of Sports Nutrition	2,138	5.068	0.002450
15	JOURNAL OF NUTRITIONAL BIOCHEMISTRY	11,460	4.873	0.011150
16	EUROPEAN JOURNAL OF NUTRITION	7,800	4.664	0.012060
17	Nutrients	32,094	4.546	0.063940
18	INTERNATIONAL JOURNAL OF OBESITY	23,347	4.419	0.024780
19	Nutrition & Diabetes	1,442	4.357	0.003670

Publication 2:

Muth AK, Losecaat Vermeer A, Terenzi D, Park SQ. The impact of diet and lifestyle on wellbeing in adults during COVID-19 lockdown. Front Nutr. 2022 Oct 6;9:993180. doi: 10.3389/fnut.2022.993180. PMID: 36276821; PMCID: PMC9582278.

Journal Data Filtered By: **Selected JCR Year: 2020** Selected Editions: SCIE,SSCI
Selected Categories: **"NUTRITION and DIETETICS"** Selected Category Scheme: WoS
Gesamtanzahl: 88 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	PROGRESS IN LIPID RESEARCH	7,328	16.195	0.004530
2	Annual Review of Nutrition	6,896	11.848	0.004410
3	CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION	23,225	11.176	0.019460
4	Advances in Nutrition	9,085	8.701	0.013170
5	NUTRITION RESEARCH REVIEWS	3,270	7.800	0.001810
6	FOOD CHEMISTRY	156,884	7.514	0.100290
7	CLINICAL NUTRITION	20,235	7.324	0.021830
8	Hepatobiliary Surgery and Nutrition	1,292	7.293	0.002280
9	NUTRITION REVIEWS	10,963	7.110	0.007650
10	AMERICAN JOURNAL OF CLINICAL NUTRITION	67,556	7.045	0.036660
11	Current Obesity Reports	2,167	6.919	0.005190
12	Frontiers in Nutrition	3,255	6.576	0.005590
13	FOOD REVIEWS INTERNATIONAL	2,961	6.478	0.001220
14	International Journal of Behavioral Nutrition and Physical Activity	14,522	6.457	0.018810
15	PROCEEDINGS OF THE NUTRITION SOCIETY	7,238	6.297	0.005090
16	JOURNAL OF NUTRITIONAL BIOCHEMISTRY	14,446	6.048	0.010580
17	Nutrients	60,526	5.717	0.090380
18	EUROPEAN JOURNAL OF NUTRITION	10,660	5.614	0.012300
19	Genes and Nutrition	2,090	5.523	0.001740

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Narrative Review

The impact of dietary macronutrient intake on cognitive function and the brain

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Inflammation

SUMMARY

Macronutrients – carbohydrates, fats, and proteins – supply the nutrients required for optimal functioning. Inadequate intake compromises both physical and brain health. We synthesized research on macronutrients from whole meals on cognitive function in healthy adults and identified underlying mechanisms. Intake of simple carbohydrates ('sugars') is consistently associated with decreased global cognition whereas consumption of complex carbohydrates correlates with successful brain aging and improved memory both in the short- and long-term. Saturated fatty acid intake correlates with decreased memory and learning scores whereas omega-3 intake correlates positively with memory scores. Protein intake boosts executive function and working memory when task-demands are high. Individual differences affecting the macronutrient-cognition relationship are age, physical activity, and glucose metabolism. Neural correlates reflect findings on cognitive functions: cortical thickness and cerebral amyloid burden correlate with sugar intake, inflammatory status and cerebral glucose metabolism correlate with fatty acid intake. Key mechanisms by which dietary macronutrients affect the brain and cognition include glucose and insulin metabolism, neurotransmitter actions, and cerebral oxidation and inflammation. In conclusion, macronutrient intake affects cognitive function both acutely and in the long-term, involving peripheral and central mechanisms. A healthy diet supports brain integrity and functionality, whereas inadequate nutrition compromises it. Studying diet can be key to nutritional recommendations, thereby improving the landscape of mental health and healthy brain aging.

1. Dietary macronutrient intake and cognitive function

The human brain requires energy and nutrients to function. Macronutrients – carbohydrates, proteins, and fats –supply glucose, fatty acids, and amino acids among others. Macronutrient intake must be balanced in a healthy diet; the WHO recommends a carbohydrate intake of 55–75%, a protein intake of 10–15%, and a fat intake of 15–30%. However, these recommendations are not met adequately [1,2].

Inadequate macronutrient intake compromises the optimal functioning of the human body. It plays a role in the development of preventable diseases such as cardiovascular disease [1,2], cancer [1], and type 2 diabetes mellitus [3]. Accumulating evidence suggests that psychological and mental health is also affected by inadequate dietary intake and can be linked to a higher risk of depression [4], dementia, and cognitive decline [5,6]. Furthermore, evidence from experimental manipulation of macronutrient compositions, such as changing the ratio of carbohydrates to protein in a single meal, has been shown to acutely affect cognitive functions [7–9].

This review aims to synthesize previous research addressing the effects of macronutrients from acute, intervention, and long-term whole meal studies on cognitive functioning in healthy young and old adults, and to understand common and distinct mechanisms by which macronutrients affect cognitive functions. In section two we present literature search findings on macronutrient

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effects on cognitive functions and the potential modulation effects of individual differences (e.g., age). First, findings on carbohydrates are presented, followed by dietary fats and proteins. In section three of this review, we explore putative mechanisms that had been identified by articles from the literature. There we examine the underlying mechanisms by which macronutrient intake affects the brain and cognition, including metabolic and neural correlates.

2. Macronutrients on cognitive function

2.1. Literature search

Searches of electronic databases were conducted between August and September 2018 via PubMed and Scopus. Search terms included macronutrient, cogniti*, carb*, glucose, protein, amino acid, fat, fatty acid, diet*, nutr*, food. To be included, studies needed to be peer-reviewed articles written in English, less than 20 years old, include healthy, non-obese adults, contain at least one measure of macronutrient intake from whole meal intake and at least one cognitive outcome or brain measure. Title and abstract screening were performed by two people. A total of 40 articles were identified this way. Papers identified through other reviews were also included (N = 6). See Fig. 1 for details of the literature search procedure.

2.2. Carbohydrates and cognitive function

Carbohydrates are different types of biomolecules made up of carbon, hydrogen, and oxygen atoms [10]. Plant whole foods provide complex carbohydrates such as starches and fibers that need to be broken down into their constituent sugars [10]. Processed foods, on the other hand, such as snack foods and sweets supply simple sugars [10]. Sugars are already broken down and provide instantly available mono- or disaccharides [10].

Generally speaking, simple carbohydrates, or sugars, are associated with worse global cognition, as assessed by cognitive test batteries that assess multiple cognitive functions [6,11,12]. For example, each 60 g of daily sugar intake lowered Mini Mental State Examination (MMSE; assessing orientation, attention span, memory, space division, verbal fluency) score by as much as 10 additional years of life [12]. In addition to these global measures [12], found that memory function negatively correlated with total sugar intake, while there was only a trend for attention but not by executive functions. Taylor and colleagues (2017) in contrast found that executive control, working memory, attention and visual-spatial processing (Trail Making Test B, WAIS-R Digit Symbol, Block Design) were also negatively correlated with sugar intake. While [6,11] did not provide data on glucose and fructose, findings from [12] provide evidence that high intake of glucose and added, but not natural, fructose is associated with poorer global cognition.

In contrast, diets rich in fiber are associated with better cognitive outcomes [13–16]. A longitudinal study with a large cohort (N = 1609) provided evidence for an association between regular higher fiber intake (29 g/day) and successful aging (defined as the absence of disability, depressive symptoms, cognitive impairment, and chronic diseases) 10 years later [15]. Thus, carbohydrate type can have opposing effects on brain function.

Different carbohydrates affect glucose metabolism to varying degrees with large inter-individual differences [17]. For individuals with normal fasting plasma glucose level (NFG; i.e., fasting glucose below 6 mmol/l), the acute amount of carbohydrate intake did not affect memory performance [18]. However, non-diabetic participants with impaired fasting glucose performed significantly poorer on a declarative memory task following a meal rich in carbohydrates [18]. Likewise, memory performance improved with the concurrent intake of at least 6 g of fiber in participants with poor glucose tolerance [18]. Dietary fiber is known to attenuate glucose metabolism [19], thereby helping to slow the release of glucose which correlates with improved memory performance [18]. Furthermore, glucoregulation and carbohydrate availability also played a role in selective attention in older [20], but not in young adults [18]. Glucoregulation refers to the body's ability to balance freely available glucose used by cells for energy and its stored form glycogen [10]. In middle-aged and older adults with good glucoregulation, a low glycemic index (GI; compares the average blood glucose response to 50 g of a carbohydrate test food with a reference food) meal led to superior sustained attentional performance using visual stimuli in contrast to a high GI meal (both in accuracy and reaction time) [20].

Elderly adults may be more susceptible to influences of carbohydrates on cognition due to a combination of impaired glucoregulatory control [21] and malnutrition [22]. Furthermore, above-

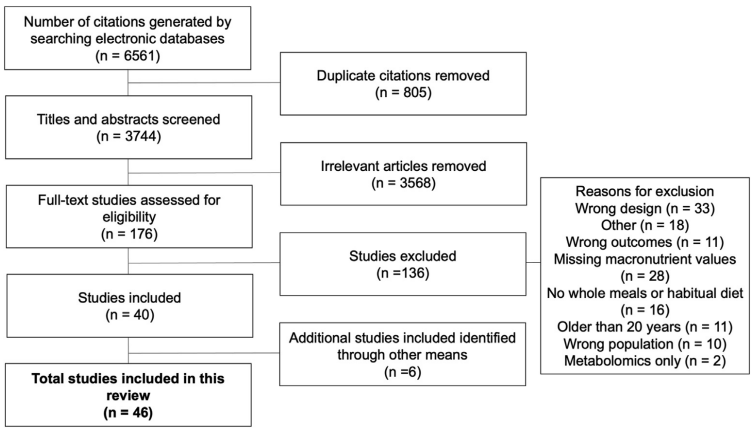

Fig. 1. Flow chart of the literature search.

average sugar intake is associated with adverse neural outcomes such as increased amyloid burden [11], reduced cortical thickness (in older adults) [23], and impaired global cognition [11,24]. Malnutrition with insufficient carbohydrate intake also correlates with poor cognitive scores in elderly adults as shown in longitudinal studies using the MMSE [22,25] and the short portable mental state questionnaire [24]. In contrast, fiber-rich diets are associated with optimal cerebral glucose metabolism [13] and ultimately better long-term outcomes, i.e., successful aging over 10 years in adults aged 49 and older [15]. Thus, age magnifies the carbohydrate effects on glucoregulation and cognition performance.

Finally, variations on the cholesterol regulator gene apolipoprotein E (APOE) may modulate cognitive performance following carbohydrate intake. Carrying the epsilon allele (ε4) is linked to higher cognitive decline per year compared to non-carriers (−0.126 standardized decline units/year compared to −0.078 units/year) [26]. Interestingly, cognitively healthy ε4 carriers seemed to benefit from a high GI meal in terms of memory performance even though cognitively impaired ε4 carriers and people without ε4 showed a negative association between acute high GI meal intake [27] and habitual carbohydrate intake [28] on memory performance. However, ε4 carriers showed poorer attention following high carbohydrate intake [28]. These studies imply that carbohydrate intake can affect attention and memory specifically in ε4 carriers. However, the mechanism by which carbohydrate intake, glucose metabolism and lipid metabolism interact via ApoE to contribute to cognitive dysfunction in Alzheimer risk are still unclear (for a review on current studies see [29]).

Taken together, these results indicate that fiber intake is associated with better cognitive performance, whereas high sugar or simple carbohydrate intake is linked with impaired cognitive functions (Table 1). As one possible underlying mechanism, glucoregulation mediates the impact carbohydrate intake has on individuals. Memory performance is highly sensitive to food-induced glucose changes. Advanced age inherently increases the risks for suboptimal glucoregulation, which increases sensitivity to carbohydrate intake, while younger people appear relatively resilient in this regard. Finally, APOE ε4 genotype, involved in fat metabolism and a known risk factor for Alzheimer's disease, modifies the impact carbohydrate intake has on memory and attention. Mechanisms by which carbohydrate intake affect cognitive functioning are discussed in detail in section three of the review.

2.3. Dietary fatty acids and cognitive function

There are four classes of dietary fats: saturated, trans, mono - and polyunsaturated fats (commonly abbreviated as MUFA and PUFA, respectively) [10]. Saturated fatty acids (SFA) are found in dairy and meat products [10]. Processed foods are high in trans unsaturated fats [10]. MUFA and PUFA are found in olive oil, nuts, avocados, vegetables, and vegetable seed oils [10]. Dietary cholesterol, an unsaturated alcohol is prevalent in meat, eggs, and dairy [10].

The literature on the effects of dietary fatty acids on cognitive functions indicates that PUFAs, which contain omega-3 and omega-6 essential fatty acids, are generally associated with cognitive benefits. Diets rich in PUFAs have been linked to improved memory [30–32] and faster psychomotor processing speed [30,33,34]. Especially omega-3 (i.e. alpha-linolenic acid which is the precursor of EPA, DPA and DHA) was shown to be beneficial for memory functions such as spatial memory and learning in a cross-sectional study in older adults [35], semantic memory in a longitudinal study with old adults [26], short-term memory and recall in an observational study with adults over 60 [36], and memory function generally in a cross-sectional study with middle-aged to old adults [37]. A cross-sectional study by Handing and colleagues showed that PUFA intake, but none of the other fatty acids, predicted delayed story recall performance using the East Boston memory task in adults aged 60 years and above [31].

On the other hand, high intake of SFA has been demonstrated in cross-sectional and longitudinal studies to lead to worsening of different cognitive functions, such as prospective memory performance [30], visuospatial learning, and verbal memory performance in young adults [38]. Similarly, habitual intake of processed foods high in trans fats predicted poorer visuospatial learning and verbal memory performance in young women [38].

The effects of cholesterol and MUFA intake on cognitive functioning are less clear. On the one hand, both have been shown to correlate with better performance on memory tasks [39], global cognitive function [25,39–41], as well as decreased risk for Alzheimer's [42] and mild cognitive impairment [43]. On the other hand, cholesterol intake was associated with suboptimal performance on global cognitive test scores and MUFA intake with worse learning and memory performance in a cross-sectional study with 3960 individuals [34]. Poor performance on the Concept Shifting

Table 1
Macronutrients impact on cognitive functions.

Macronutrient			Findings
Carbohydrate	Simple		↓ Global cognition [6,11,12,24]
	Fiber		↑ Successful aging [15], memory [18]
			↓cognitive decline [16]
Fat	Saturated fatty acids		↓ Memory [30,38], learning [38]
	Unsaturated fatty acids	MUFA	↑ Memory [39,40] global cognition [39]
			↓ cognitive decline [41], MCI risk [42,43,62], Memory [34,44]
		PUFA	↑ Memory [26,30–32,35–37] faster psychomotor processing [30,33,34]
		Trans fats	↓ Memory [38], learning [38]
			↑ cognitive decline [49]
	Cholesterol		↑ Global cognition [25,41]
			↓ Global cognition [34] learning [33]
Protein	Short-term		↑ Inhibition control [50,51] faster reaction time on demanding task [50]
	Long-term	Adequate consumption	↑ Fluid intelligence [52] working memory [52,53] memory [52] global cognition [22]
			- Memory [31] global cognition [25,58]
		Over- and under consumption	↓ Digit subtraction [31] working memory [60]
			Risk of Mild Cognitive Impairment [14]

The effect of carbohydrates and fat intake on cognitive function is specific to the cognitive domain, depending on the task, subtype of macronutrient (e.g., simple versus complex carbohydrates), and the population's age. Acute protein intake boosts cognitive function under taxing conditions and in the long-term adequate levels of protein intake are linked to intact cognitive performance. ↑ indicates better performance; ↓indicates worse performance; - indicates no difference in performance. MCI mild cognitive impairment.

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task, the Stroop test, and a visual-verbal learning task were related to higher cholesterol intake in both middle-aged and older adults [33], and high MUFA intake was predictive of mild cognitive impairment in middle-aged adults [44].

Interestingly, physical activity may attenuate the adverse effects of SFA intake on cognition [45]. A cross-sectional study showed that former athletes who consumed high amounts of SFA did not suffer from self-reported cognitive difficulties [45]. Indeed, diet and exercise jointly affect energy homeostasis and synaptic plasticity as evidenced by human and animal studies [46]. The benefits of docosahexaenoic acid (DHA belonging to omega-3 fatty acids) intake are further increased by concurrent exercise [47]. Even more so, exercise can ameliorate the negative effects of a high-fat diet on synaptic plasticity via brain-derived neurotrophic factor as shown in rodents [48].

Genotype may account for discrepant findings. Carriers of $\varepsilon 4$ may not benefit from PUFAs the way that non-carriers do. Instead, higher PUFA intake (20–30 g/day) in carriers was associated with higher, potentially detrimental, levels of cerebral glutamate, which is necessary for learning and memory but is neurotoxic at high concentrations [32]. People with the $\varepsilon 4$ allele seemed to benefit from 1) medium intake (0.07 g/day) of omega-3 PUFAs DHA and eicosapentaenoic acid from seafood and 2) higher intake of the plant-based omega-3 alpha-linolenic acid, as evident through attenuated cognitive decline [26].

Dietary fatty acids affect cognitive functions following a pattern: SFA, trans fat, and cholesterol are largely associated with impaired functioning while MUFA and PUFA intake are generally beneficial (Table 1). This was especially true for executive function, memory, and overall cognitive performance. Thus, the studies need to specify the type of dietary fat to investigate their specific effects on cognition. In the elderly, high fat intake is related to dementia risk [30,49], whereas PUFA and MUFA intake may act protectively [26,31,35,42,43].

2.4. Protein and cognitive function

Proteins are the building blocks of bones, muscles, skin, and blood and make hormones and neurotransmitters. Dietary protein may be plant- or animal (incl. animal byproducts such as eggs or dairy) derived. Animal-derived proteins contain adequate proportions of all essential amino acids, making them complete proteins. Plant proteins, on the other hand, are incomplete proteins with some exceptions like soybeans. Digestion breaks down proteins into amino acids which have multiple purposes in the body [10]. Of particular interest are tryptophan and tyrosine: both play key roles in cognitive functioning as they are precursors to dopamine and serotonin (see also *Neurotransmitter actions*).

Results from a 21-day high protein dietary intervention (3 g/kg body weight of animal-derived protein per day compared to usual protein intake) revealed benefits for inhibition on the go/no go task following the intervention period [50,51] as well as for reaction times on a relatively demanding task that requires cognitive control to withhold undesired responses, but not on a less demanding sustained attention task [50]. These results suggest that protein may boost task performance on more complex tasks.

Furthermore, evidence from longitudinal and cross-sectional studies showed that tyrosine levels via protein intake were significantly correlated with fluid intelligence (based on a composite score derived from performance on figural analogies, letter series, and practical problems) [52] and working memory (based on a composite score assessing letter updating, n-back, and spatial updating) in both old and young people [52,53]. However, a negative association between high protein intake and digit subtraction has also been reported in older adults [31]. The authors proposed that this negative finding is likely due to a concurrent increase in fibrinogen, an inflammatory biomarker associated with cardiovascular disease and dementia risk [31].

Results regarding long-term memory might be function-specific. Kühn found a positive relationship between protein intake and episodic memory tasks such as the face-profession task and scene encoding in young and old people [52] while there was no association between protein intake and semantic memory [31]. This might be driven by the high correlation of tryptophan with tyrosine levels [52]. Both amino acids have been shown in depletion studies to play a role in long-term memory: tryptophan is involved in declarative memory consolidation whereas tyrosine plays a role in spatial memory [54]. Besides, other nutrients present in food, such as B vitamins [55], may confound findings and account for the protein-cognition improvement [51,52].

Cognitive difficulties in the elderly may in part be due to inadequate protein consumption. Indeed, most studies found a positive correlation (r ranging from 0.18 to 0.29) between protein intake in the elderly and global cognitive functioning [22,56,57], whereas other studies reported null findings [25,58]. Habitual protein intake as a protective factor seems to attenuate cognitive decline in old age [22,52,56,57] and to reduce the incidence of mild cognitive impairment or dementia together with PUFA intake [6]. Kühn and Hensel presented evidence that the average daily intake of tyrosine in older adults was 2.8 g [52,53], which is significantly below the WHO recommendation [53].

Overconsumption of protein may be as detrimental as insufficient intake. Evidence from a recent study in older adults (age > 65 years) found that high protein intake (>16.5% of total energy intake) was associated with an increased incidence of mild cognitive impairment compared to individuals with normal protein intake (15% and below) [14] which corresponds to the protein intake goal recommended by the WHO [59]. Similarly, excessive tyrosine intake, which increases with greater protein intake, correlated with decreased working memory performance as measured by the 3-back task (but not with lower working memory loads) in older adults [60]. It is noteworthy that the administered tyrosine doses of 100–200 mg/kg body weight were much higher than the minimum recommended level by the WHO (25 mg/kg/day) [61].

In sum, protein intake selectively enhances working memory and episodic memory (but not semantic memory), primarily when task demands are high (Table 1). Especially in advanced age, adequate protein intake is crucial as both insufficient and excessive protein intake has been associated with adverse outcomes.

3. Mechanisms underlying the effects of macronutrients on the brain

Dietary macronutrient intake impacts multiple mechanisms, pointing to different pathways linking dietary macronutrient intake and cognitive function. Some of these pathways underly acute functional changes, such as peripheral and central glucose and insulin metabolism or neurotransmitters. On the other hand, oxidation and inflammation can lead to long-term influences, such as structural brain damage. Here, we review those evidences for pathways and mechanisms in more detail (Fig. 2).

3.1. Glucose and insulin metabolism

Glucose and insulin metabolism are tightly linked and are known to act in the brain as neuromodulators [63]. Cerebral insulin is involved in many important functions such as gene transcription, neuroendocrine function [64], neurotransmitter regulation such as norepinephrine [65], as well as serotonergic [66] and dopaminergic

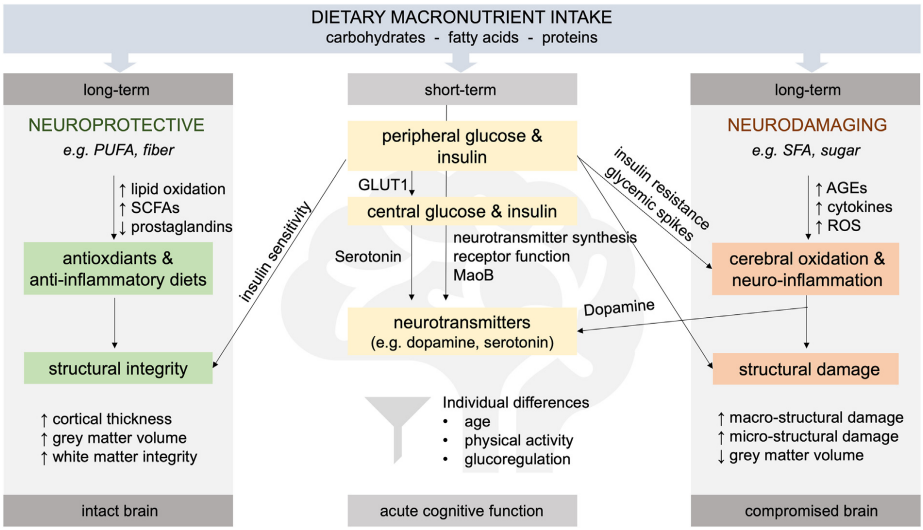

Fig. 2. Macronutrient intake affects the brain and cognitive function via multiple pathways both acutely and long-term. Acute effects of macronutrient intake affect peripheral and central glucose and insulin metabolism via glucose transporter 1 (GLUT1), as well as neurotransmitter synthesis. These effects depend on individual differences including age, genotype, physical activity, and glucoregulation. Long-term effects can be either neuroprotective or neurodamaging, depending on the subtype of carbohydrate and fatty acid. Macronutrients that are associated with neurodamaging effects lead to cerebral oxidation and inflammation thereby leading to structural damage over time. Intake of macronutrients associated with neuroprotective effects helps to retain structural integrity. AGEs advanced glycation endproducts, GLUT1 glucose transporter 1, MaoB monoamine oxidase, PUFA polyunsaturated fatty acids, ROS reactive oxygen species, SCFA short-chain fatty acids, SFA saturated fatty acids.

signaling [67]. For instance, rising levels of insulin can trigger the release of striatal dopamine [68]. Cerebral insulin plays a role not only in homeostatic maintenance [69] but also in cognitive functions like memory, learning [70]], mood [71] and reward processing [67]. Impaired insulin metabolism is linked to mitochondrial dysfunction [67,72] and micro-structural aberrations [73] in the brain, and downregulated dopamine signaling as well as depressive-like symptoms in rodents [73]. Impaired glucose metabolism is linked to oxidative stress [69] and inflammation [70] (see also *Oxidative stress and inflammation*) as well as macro-structural changes [73]. Thus, a dysfunctional glucose and insulin metabolism leads to a cascade of detrimental consequences that play into the vicious cycle linking metabolic dysfunction and cognitive impairment [70,71].

Dietary fat intake also impacts peripheral glucose tolerance and insulin regulation in the short- and long-term [74–77]. A prolonged high-fat diet, typically rich in saturated and trans fats, reduces the expression of the glucose transporter GLUT1, responsible for cerebral glucose uptake [78], which induces memory impairments in rodents [79]. This is supported by tentative evidence for worsened speed of retrieving memories in humans following a short-term high-fat diet intervention [80]. PUFA intake, on the other hand, is associated with improved insulin sensitivity [81] and, as shown above, is associated with improved memory and processing speed. Additionally, fatty acids also act directly on brain glucose metabolism [79], which is predictive of Alzheimer's disease development [69]. Omega-3 and omega-6 intake was positively associated with glucose metabolism (as measured by fluorodeoxyglucose uptake using positron emission tomography) in the medial, inferior, and lateral frontal cortex [13]. In contrast, saturated fat intake was negatively associated with glucose metabolism in the middle and inferior temporal cortex bilaterally, right frontal cortex, and left parietal cortex [13].

It has been debated, whether a high or low protein diet can improve glucoregulation. Systematic reviews and meta-analyses have not reached a decisive answer, as there is large heterogeneity between studies [82], low compliance, and high dropout rate [83].

In sum, glucose and insulin metabolism can have profound influences on brain activity, notably, through modulation of neurotransmitter signaling which affects cognition. Impaired glucose and insulin metabolism are linked to oxidative stress and inflammation in the brain as well as structural aberrations (see also *Oxidative stress and inflammation*).

3.2. Neurotransmitter actions

Tyrosine and tryptophan, two large neutral amino acids (LNAA), are precursors of dopamine and serotonin respectively and compete for entrance to the blood–brain-barrier together with other LNAAs [84]. Both the carbohydrate to protein ratio, as well as the type of protein acutely affect the balance of amino acids in the blood [85] and brains of rodents [86].

Studies manipulating or observing macronutrient intake have provided evidence for dietary-induced neurotransmitter actions on cognitive functions and behavior [87]. A high protein intake impacts social decision-making via tyrosine metabolism. A meal with a high protein/carbohydrate ratio reduced rejection rates to unfair offers in the ultimatum game [88]. The reduction of rejection rates could be predicted by the enhanced tyrosine/LNAA ratio manipulated by meal composition (high protein versus low protein meals) [88].

Fat intake can also directly influence serotonin levels in the brain via tryptophan synthesis [89], and indirectly via insulin (see above) [63]. For instance, eicosapentaenoic acid (EPA; contained in omega-3 fatty acid) regulates serotonin release from presynaptic neurons by reducing prostaglandins [90]. Furthermore, docosahexaenoic acid (DHA) regulates serotonin receptor function by

increasing membrane fluidity [91] and thereby serotonin receptor accessibility in postsynaptic neurons [89]. Thus, the essential fatty acids DHA and EPA play a key role in serotonin function and provide the link between the cognitive benefits of omega-3 intake and serotonin levels [89]. Similarly, rodents on high-fat diets showed reduced dopamine transporter receptor binding density and turnover in the nucleus accumbens and striatum, which is a sub-cortical structure [92,93].

Different amino acids can acutely affect cognitive functions distinctly. For instance, faster reaction times on a complex attention task were driven by increased branched-chain amino acids as well as plasma tyrosine and phenylalanine concentration (a tyrosine precursor), which are crucial for dopamine and norepinephrine synthesis [50]. Furthermore, protein intake is implicated in regulating monoamine oxidase (MAOB) which breaks down dopamine. Zellner observed a 26% decrease of MAOB expression following a 21-day high protein diet. The authors discussed the possibility that both an increase in dopamine synthesis due to higher phenylalanine availability [50] and a lower metabolic rate of dopamine attributed to decreased MAOB activity may have caused the boost in reaction time on a cognitively demanding but not on a simple task [51]. This is in line with findings from tyrosine loading studies showing that tyrosine counteracts performance decrements under physically and mentally taxing conditions by recharging exhausted brain catecholamine levels [94].

Generally, there are dose-dependent effects of protein whereby optimal habitual dietary tyrosine intake seems to be beneficial in older people [52,53] and maybe mediated by downregulated MAOB expression, which is involved in dopamine breakdown [51]. Cognitive detriments due to insufficient protein intake in an older population could be explained by the depletion hypothesis: older people may be particularly vulnerable to inadequate protein consumption due to decreased brain dopamine receptor and transporter binding [95]. In contrast, performance declines due to excessive protein consumption may be accounted for by the overdose hypothesis, postulating that detriments may be caused by increased dopamine synthesis capacity in the elderly [96–98]. Thus, adequate protein intake is particularly important for the elderly.

Besides serotonin and dopamine, other neurotransmitters are also affected by macronutrient intake, such as glutamate [99], the major excitatory neurotransmitter that plays an important role in memory and learning [100]. High PUFA intake may be protective from future cognitive decline and was associated with lower cerebral glutamate [32], which may be neurotoxic [101].

In sum, dietary macronutrient intake affects cognitive functions and behavior via neurotransmitters directly, and in the case of serotonin indirectly via insulin metabolism. Most elucidated are effects on dopaminergic and serotonergic pathways via tyrosine and tryptophan. Dose-dependent effects of tyrosine point to the importance of adequate protein intake, especially in old age.

3.3. Oxidative stress and inflammation

Oxidation is a process whereby mitochondria release adenosine triphosphate (ATP), the main fuel of cells [102]. Reactive oxygen species (ROS, or free radicals) are a by-product of this process, and while low to moderate levels are tolerable, excessive amounts cannot be neutralized by antioxidants and cause oxidative stress to the brain, further leading to cellular degeneration [103] predicting cognitive decline over 4 years [104].

Acute peripheral inflammation is an immune response aimed at wound healing [105]. However, sustained inflammation correlates with age and obesity and can be due to unhealthy lifestyle factors such as diet, smoking, and stress. For instance, recurrent postprandial hyperglycemia can cause inflammation due to an overproduction of reactive free radical molecules and the response of inflammatory cytokines [106].

Neuroinflammation, i.e., inflammation in brain tissue is also marked by a rise in immune markers such as the cytokines interleukin, c-reactive protein, and tumor necrosis factor and affects behavior, e.g., depressive and sickness behavior [107,108]. While peripheral and neuroinflammation have commonalities and can exacerbate one another, they are considered distinct processes [109]. Hypothalamic inflammation is implicated in insulin and leptin resistance in the arcuate nucleus, and disrupts metabolic feedback, thereby promoting hyperphagia and weight gain [110]. Other brain structures, including the hippocampus, cortex, cerebellum, and amygdala are also affected by diet-induced neuroinflammation [109], linking diet-induced metabolic diseases with cognitive deficits (Fig. 2).

Inflammation and oxidative stress are affected by dietary intake and play a pivotal role in long-term cognitive outcomes and successful brain aging [111–114]. For instance, it has been shown that poor glucose and insulin regulation contribute to neuroinflammation and oxidative stress in the brain [115,116] leading to neurodegeneration [117], dementia [117], depression, and mild cognitive impairment.

Additionally, poor glucose and insulin metabolism are associated with structural changes. Structural changes in the brain are linked to dementia risk and there is strong evidence that an unhealthy diet is linked to vascular damage [118]. For instance, a study on non-diabetic elderly participants found that macro-structural damage (including atrophy) correlated with higher fasting glucose, and micro-structural aberrations (detected via magnetization transfer imaging) correlated with measures indicating reduced insulin sensitivity [73].

Furthermore, high intake of sugar fosters inflammation and oxidative stress via cerebral accumulation of Advanced Glycation Endproducts (AGEs) [119]. In contrast, low intake of high GI foods reduces inflammation due to the absence of glycemic spikes which induce oxidative stress [120]. Whether fiber intake ameliorates inflammation is less clear, due to confounds that correlate with high fiber intake which covary with other healthy lifestyle habits [120]. Possible pathways by which fiber intake might decrease inflammation are: (1) increased lipid oxidation and (2) short-chain fatty acids produced by fermentation of fiber in the gut [121,122] see also *Gut-brain axis*.

Dietary fats also affect cognition via pro- or anti-inflammatory processes by activating microglia (dubbed the immune cells of the central nervous system). Short-chain fatty acids produce inflammatory mediators such as cytokines and reactive oxygen species [123]]. Omega-3 fatty acids such as EPA and DHA play an important role in the inflammatory response. They are precursors for the formation of pre-resolving mediators such as resolvins, protectins and maresins, which actively resolve inflammation [124]. This mechanism is also found in the brain, significantly influencing neuroinflammation [125].

In contrast, saturated fatty acids and monounsaturated fatty acids are pro-inflammatory [109]. The role of omega-6 in this respect is not yet well understood [126]. Inflammatory responses can be very quickly induced: a three-day high-fat diet was shown to foster transient inflammation in a mouse model [127], while a long-term high-fat diet leads to prolonged inflammation that fosters cellular stress [110] and induces apoptosis of hypothalamic neurons [128]. The link between central inflammation and cognition has been substantiated by evidence from animal studies [129]. Evidence from human studies so far is lacking, however, one study could show the link between inflammatory markers in the occipitoparietal grey matter and memory performance [130].

increasing membrane fluidity [91] and thereby serotonin receptor accessibility in postsynaptic neurons [89]. Thus, the essential fatty acids DHA and EPA play a key role in serotonin function and provide the link between the cognitive benefits of omega-3 intake and serotonin levels [89]. Similarly, rodents on high-fat diets showed reduced dopamine transporter receptor binding density and turnover in the nucleus accumbens and striatum, which is a sub-cortical structure [92,93].

Different amino acids can acutely affect cognitive functions distinctly. For instance, faster reaction times on a complex attention task were driven by increased branched-chain amino acids as well as plasma tyrosine and phenylalanine concentration (a tyrosine precursor), which are crucial for dopamine and norepinephrine synthesis [50]. Furthermore, protein intake is implicated in regulating monoamine oxidase (MAOB) which breaks down dopamine. Zellner observed a 26% decrease of MAOB expression following a 21-day high protein diet. The authors discussed the possibility that both an increase in dopamine synthesis due to higher phenylalanine availability [50] and a lower metabolic rate of dopamine attributed to decreased MAOB activity may have caused the boost in reaction time on a cognitively demanding but not on a simple task [51]. This is in line with findings from tyrosine loading studies showing that tyrosine counteracts performance decrements under physically and mentally taxing conditions by recharging exhausted brain catecholamine levels [94].

Generally, there are dose-dependent effects of protein whereby optimal habitual dietary tyrosine intake seems to be beneficial in older people [52,53] and maybe mediated by downregulated MAOB expression, which is involved in dopamine breakdown [51]. Cognitive detriments due to insufficient protein intake in an older population could be explained by the depletion hypothesis: older people may be particularly vulnerable to inadequate protein consumption due to decreased brain dopamine receptor and transporter binding [95]. In contrast, performance declines due to excessive protein consumption may be accounted for by the overdose hypothesis, postulating that detriments may be caused by increased dopamine synthesis capacity in the elderly [96–98]. Thus, adequate protein intake is particularly important for the elderly.

Besides serotonin and dopamine, other neurotransmitters are also affected by macronutrient intake, such as glutamate [99], the major excitatory neurotransmitter that plays an important role in memory and learning [100]. High PUFA intake may be protective from future cognitive decline and was associated with lower cerebral glutamate [32], which may be neurotoxic [101].

In sum, dietary macronutrient intake affects cognitive functions and behavior via neurotransmitters directly, and in the case of serotonin indirectly via insulin metabolism. Most elucidated are effects on dopaminergic and serotonergic pathways via tyrosine and tryptophan. Dose-dependent effects of tyrosine point to the importance of adequate protein intake, especially in old age.

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foods, including fresh fruit, vegetables, legumes and whole grains which supplies fiber and limits sugar intake; (3) includes plenty of MUFA and PUFA intake from regular seafood and vegetable-based oils while avoiding high intake of saturated fats and trans fats.

This also is consistent with the World Health Organization's recommendations to reduce the risk of noncommunicable diseases such as heart disease, stroke and cancer [170]. The information sheet by the WHO also provides dosage recommendations and how to achieve such a healthy diet on a sustainable level [170].

Limitations of the current studies include few interventional studies and large heterogeneity between studies. For instance, discrepancies in findings for cholesterol and MUFA may be due to differences in methodology (e.g., 24-h recall of dietary intake compared to use of a food frequency questionnaire) [34], statistics (e.g., use of linear versus logistic regression) [34], or cultural and sociodemographic contexts [44]. Finally, other dietary factors, such as total caloric intake and overall quality of the diet may also affect the outcome; high total caloric intake is associated with increased inflammation levels and several negative health outcomes [44].

Future studies ought to consider the integrative nature of diet on the brain and behavior. For instance, interventional studies of diets with extreme macronutrient compositions, such as very high protein intake, may not be feasible and lack ecological validity. Macronutrient intake exists in a dietary context, meaning that nutrients are often processed and consumed alongside other nutrients. The concept of food matrix considers the interactions of all nutrients and components that make up a food. Thereby it determines the bioavailability and biological activity of the individual nutrients such as release and utilization of macronutrients and their associated physiological response [171]. For example, the presence of dietary fiber lowers the utilization of carbohydrates. As a consequence, concurrent fiber intake attenuates blood sugar increase. Thus, as a future direction it would be useful for the study of nutritional psychology and neuroscience to integrate food matrices and control for their effects.

Finally, while some individual differences such as age, education, (mental) health status are already being taken into consideration when analyzing results, others, such as genetics and microbiome, are just beginning to be understood. However, they may be key in providing optimal nutritional recommendations, and ultimately in improving the landscape of mental health and healthy brain aging.

Funding statement

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Author contribution

Anne-Katrin Muth: conceptualization, data collection, data analysis and interpretation, writing – original draft preparation, visualization. **Soyoung Q Park**: conceptualization, funding acquisition, resources, supervision, data interpretation, writing – review & editing.

Conflict of interest

The authors are unaware of any conflicts of interest.

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Author contribution

Anne-Katrin Muth: conceptualization, data collection, data analysis and interpretation, writing – original draft preparation, visualization. **Soyoung Q Park**: conceptualization, funding acquisition, resources, supervision, data interpretation, writing – review & editing.

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The impact of diet and lifestyle on wellbeing in adults during COVID-19 lockdown

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A healthy diet and lifestyle may protect against adverse mental health outcomes, which is especially crucial during stressful times, such as the COVID-19 pandemic. This preregistered longitudinal online study explored whether diet and lifestyle (physical activity, sleep, and social interactions) were associated with wellbeing and mood during a light lockdown in Germany. Participants (N = 117, 72 males; 28 ± 9 years old) answered mental health and lifestyle questionnaires (social connections, sleep, activity) followed by submitting 1 week of food and mood-lifestyle diary (food intake, positive and negative mood, mental wellbeing, sleep quality, physical activity level, quantity and quality of social interactions) *via* a smartphone app. We used multivariate linear and mixed-effects models to associate mood and wellbeing with dietary components and lifestyle factors. Interindividual analyses revealed that sleep and social interaction significantly impacted mood and wellbeing. Interestingly, fruit and vegetable intake correlated with wellbeing, even when controlling for all lifestyle factors. Fruit and vegetable intake also significantly correlated with daily fluctuations in wellbeing within individuals next to sleep, physical activity, and social interactions. We observed gender differences in fruit and vegetable intake and anxiety levels. Our results emphasize the importance of diet contributing to individual wellbeing, even in the challenging times of a pandemic. Future research is necessary to test if our findings could extend to other populations.

KEYWORDS

eating behavior, mental health, COVID-19, gender, activity

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Introduction

COVID-19 lockdowns and social isolation have taken a toll on mental wellbeing (1–3). Lifestyle factors, including diet and physical activity, are shown to effectively reduce the risk of mental health disorders (4). However, it is unclear whether and how such lifestyle factors contribute to mental wellbeing during the pandemic.

A diet high in fruit and vegetables reduced depression risk (5–7) and anxiety (8). On the other hand, diets high in trans fatty acids from processed foods (9) and fast food increased depression risk over 6-years (10, 11). Dietary intake can have relatively instant effects on mood and wellbeing. Studies investigating daily associations found that higher fruit and vegetable intake was associated with wellbeing (12) and positive mood the same day or the next day (13). While eating salty snacks correlated with higher negative mood the next day in people with a high Body Mass Index (BMI) (13). Similarly, higher saturated fat intake correlated with negative mood 2 days later in college students (14).

Importantly, diet-induced neuroinflammation is a key mechanism linking diet, cognitive function, and even gray matter volume loss (15). The dietary inflammatory index (DII) estimates a diet's inflammatory potential (16), and at least two meta-analyses have established a link with depression (17, 18), depressive symptoms, anxiety, and psychological distress (19, 20). Importantly, DII and mental health profiles were less associated in men than in women (19), pointing to gender differences.

Besides diet, physical activity and sleep play a major role in wellbeing (21, 22), depression (23), anxiety (24, 25) and sleep quality (26). However, the pandemic has impacted lifestyle behaviors. For example, a recent study demonstrated that roughly 53% of 5,000 participants reported a change in activity level during the COVID-19 pandemic (27). Sleep disturbances were reliably associated with the risk for depressive symptoms and clinical depression (4) and correlated positively with mental health issues (28), suggesting that physical activity and sleep quality majorly contribute to wellbeing and mood during the pandemic.

Managing the COVID-19 pandemic required social distancing, making the link between social interaction and mental health outcomes of high interest. Social interaction is vital for mental health outcomes, including wellbeing and symptoms of depression or anxiety (29–31). For example, loneliness, the subjective feeling of the absence of a social network or a companion, is associated with adverse physical and mental health outcomes (30) and low physical activity levels in mental health patient groups (32, 33). During COVID-19-lockdown, social distancing restrictions led to increased feelings of social isolation, which coincided with more severe mental health outcomes (34). At the same time, a good relationship quality was crucial in maintaining mental health (3). Furthermore, wellbeing during the pandemic was associated with satisfaction of psychological needs at an inter- and intrapersonal level (35). Data from an Italian study during lockdown and when some restrictions were lifted showed that both emotional eating and binge-eating were increased in the presence of emotional distress, including higher levels of anxiety and depression, but also partially correlated with relationship quality and quality of life (36). An interesting question that remains is to what extent dietary intake can ameliorate the negative consequences of living through a pandemic in the context of physical activity, sleep, and social interaction quality.

In this preregistered online study,[1] we investigated whether diet, lifestyle factors, and social interaction were associated with wellbeing, anxiety, and feeling of excitement during COVID-19 lockdown. We hypothesized that food intake (i.e., fat, carbohydrates, fruit and vegetables) contributes significantly to (1) individual wellbeing, (2) anxiety, and (3) excitement, even when controlling for lifestyle factors. Next to these preregistered analyses, we tested whether inflammation, as a possible mechanism, plays a role in the relationship between food intake and wellbeing.

Materials and methods

Participants

We recruited participants *via* the online research platform Prolific. German-speaking individuals without prior mental health diagnoses, residing in Germany at the time of the study, with an Apple or Android smartphone for using the FoodApp, were eligible to participate. We excluded participants who showed above-threshold depressive symptoms (i.e., above 30, which is classified as "severe") determined by the Beck Depression Inventory [BDI; German version (37)]. Questionnaires were completed online on the SoSci Survey platform. The food and mood diary records were recorded using the FoodApp available for Android and Apple smartphones. Participants provided informed consent and received £28 for participation. Ethical approval was obtained from the Humboldt University of Berlin.

Study design

We conducted an online study using questionnaires assessing mental health, wellbeing, and lifestyle factors. Afterward, participants kept a food and mood diary and a record of sleep quality, activity, and social interactions for 7 days (**Figure 1**). In particular, in this study we wanted to

1 https://osf.io/nqhjf

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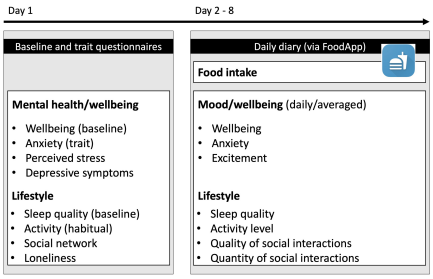

FIGURE 1
Study outline. Participants first answered questionnaires assessing baseline mental health and wellbeing as well as lifestyle-related questionnaires. Next, they completed a daily food, mood, and lifestyle diary for 7 days *via* a smartphone app.

investigate the relationship between food intake as independent variables (i.e., fruit and vegetable, fat and carbohydrate intake) and mood (i.e., wellbeing, anxiety, excitement) as dependent variables while controlling for lifestyle factors (i.e., activity, sleep and social interaction quality and quantity). Data were collected between 11 and 24 November 2020 at which time there was a light lockdown in Germany. During this time, people were asked to reduce social contacts to the minimum. In public, one was only allowed to meet with people of one's household and one additional household (from: 28.10.2020).[2]

Assessment of food-mood and lifestyle diary

The food-mood and lifestyle diaries were completed using a smartphone FoodApp for 7 days [following (14)]. For food intake, we recorded the following information: date, time, type of meal, companionship during the meal, food items, and weight consumed. Food items could be chosen from a list of about 10,000 food and beverage items commonly available in Germany, for example, "potatoes peeled boiled" or "wholemeal bread with margarine and currant jam." Participants chose the food item matching their consumption along with an estimate of how much they consumed in grams or milliliters. Participants were free to log their food intake after a meal, or later during the day. A reminder was sent to participants who did not submit their data by 7 p.m. that day. Dietary intake was evaluated using the German Federal Food Key data table [Bundeslebensmittelschlüssel (38)] made available by the Max-Rubner Institut (MRI). Data from days with extreme daily caloric intake were excluded from analysis (for women: $<$ 500 or $>$ 3,500 kcal/day, for men: $<$ 800 and $>$ 4,000 kcal/day considered as unrealistic amounts) following (39).

For dietary intake, we calculated energy-adjusted (ea) values to account for an individual's total energy intake (i.e., g/1,000 kcal/day) as suggested by Agnoli et al. (40). Additionally, we computed daily energy derived from each macronutrient. For this, we multiplied the daily intake of carbohydrate and protein (g/d) by 4 kcal, and fat intake by 9 kcal (**Table 1**). Outliers in dietary data were winsorized separately for men and women.

Finally, we calculated the Dietary Inflammatory Index (DII) score for each participant following (16). First, we selected the nutrients available to us, then we calculated z-scores by subtracting the standard global mean and dividing by the global standard deviation (the standard global mean and deviation are both found in **Table 2** of Shivappa et al. (16). Then, we converted these z-scores to normal percentiles and multiplied them by 2, and subtracted them by 1. Each score was multiplied by its respective inflammatory effect score. Lastly, all scores were summed up to derive the overall DII score for each participant.

Mood and lifestyle ratings were unlocked after 5 p.m. each day. Participants rated their wellbeing [using the short Warwick-Edinburgh Mental Wellbeing Scale (41)], anxiety, and excitement levels on a 5-point Likert scale. We added excitement and anxiety to daily measures to supplement functional wellbeing. Finally, sleep quality, activity level, quantity, and quality of social interactions were rated on a scale from 1 to 100.

Questionnaires

We used the Warwick Edinburgh Mental Wellbeing Scale [WEMWBS (41)] to assess baseline wellbeing. This 14-item questionnaire assesses different aspects of positive mental health including balance of feeling and functioning. Example items include, "I've been feeling optimistic about the future" and "I've been thinking clearly." We used the 7-item short form of the WEMWBS to assess daily wellbeing during the week of food-mood-lifestyle diary entries. This scale emphasizes functioning items over feeling items. Both versions are responsive to change (42).

Participants also completed mental health and lifestyle questionnaires, including trait anxiety [STAI (43)], depressive symptoms [BDI; German version (37)], and perceived stress [PSQ (44)]. Finally, the Community Assessment of Psychic Experiences (45) was analyzed as part of a separate study.

Statistical analyses

All data was downloaded from the FoodApp server, Prolific, and SoSci survey and imported into R studio. Plots were made using ggstatsplot (46). We reported descriptive statistics for demographic characteristics, food intake, daily ratings as well as baseline and trait questionnaire scores.

2 https://www.bundesregierung.de/breg-de/themen/coronavirus/corona-massnahmen-1734724

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TABLE 1 Sample characteristics by gender.

	Total (N = 117)[a]	Women (N = 45)[a]	Men (N = 72)[a]	p-value[b]
Age	28.12 (8.91)	30.76 (10.44)	26.47 (7.42)	**0.009**
BMI	24.21 (4.18)	23.50 (4.27)	24.65 (4.09)	**0.016**
Daily averaged food intake				
Kilocalories	1,727.09 (504.04)	1,513.31 (437.25)	1,860.71 (499.53)	<**0.001**
Protein% of kcal	16.44 (4.26)	15.27 (2.62)	17.17 (4.89)	**0.020**
Carbohydrate% of kcal	47.85 (6.79)	48.49 (7.20)	47.44 (6.54)	0.4
Fat% of kcal	34.47 (6.59)	34.81 (7.90)	34.25 (5.67)	0.8
Fruit and vegetable (g/1,000 kcal)	73.82 (43.70)	91.96 (35.17)	62.48 (44.89)	**0.009**
Dietary inflammatory score	0.00 (1.92)	0.15 (1.86)	−0.09 (1.97)	0.6
Daily averaged mood and lifestyle factors				
Wellbeing	22.26 (2.84)	22.11 (3.01)	22.35 (2.75)	>0.9
Excitement	3.07 (0.64)	3.01 (0.74)	3.10 (0.56)	0.6
Anxiety	1.88 (0.66)	2.10 (0.65)	1.74 (0.64)	**0.003**
Sleep quality	60.89 (17.42)	57.75 (17.26)	62.86 (17.36)	0.2
Activity level	41.21 (18.82)	43.09 (16.31)	40.04 (20.25)	0.3
SI[c] quality	64.22 (14.26)	67.56 (14.92)	62.14 (13.52)	**0.021**
SI[c] quantity	52.79 (19.10)	56.62 (18.36)	50.39 (19.29)	0.14
Baseline and trait questionnaires				
Baseline wellbeing	46.35 (9.05)	45.42 (9.33)	46.93 (8.89)	0.5
Trait anxiety	41.38 (12.15)	44.51 (12.54)	39.42 (11.57)	**0.035**
Depressive symptoms	9.26 (6.19)	10.13 (6.77)	8.71 (5.77)	0.4
Perceived stress	43.85 (18.18)	47.81 (18.81)	41.37 (17.45)	0.12

[a]Mean (SD); n (%).
[b]Wilcoxon rank-sum test; Pearson's Chi-squared test; Fisher's exact test.
[c]Social interaction. The bold values mean $p < 0.05$.

Weekly averages of daily data

First, we examined between-person relationships with each averaged daily dependent variable (wellbeing, anxiety, and excitement) separately. Independent variables were fruit and vegetable, fat and carbohydrate intake and lifestyle behaviors (i.e., activity, sleep, social interaction). We performed multiple linear regression using the *stats* package (47). The full models were specified as shown in equation (1). Gender was dummy-coded.

$$(1)\ \mathrm{DV} \sim \text{fruit \& vegetables} + \text{fat} + \text{carbohydrate} + \text{activity} + \text{sleep} + \text{quality of social interaction} + \text{quantity of social interaction} + \text{gender}$$

Mediation analyses

To investigate if averaged daily measures of lifestyle mediated an effect of fruit and vegetable intake on wellbeing, we performed simple mediation analyses using the *MeMoBootR* package (48). We wanted to conduct three separate mediation analyses for the outcome variable wellbeing. The mediator variables were averaged from the daily diary; (1) physical activity, (2) sleep, and (3) social behavior. Covariates were, fat, carbohydrate, sleep, quality and quantity of social interaction, and gender.

Daily and lagged analyses

Next, we performed same-day and 1- and 2-day lagged analyses to test intra-individual relationships between dependent variables (daily wellbeing, anxiety, excitement) and independent variables (i.e., fruit and vegetable, fat and carbohydrate intake) using multilevel modeling using the lme4 package (49). We included fruit and vegetable, fat and carbohydrate each as the level-1 independent variables and daily wellbeing, anxiety, excitement each as the level-1 outcome. We also included the dependent variable's score of the previous day as a covariate ($\mathrm{DV_{T0}}$).

We assessed same-day associations between fruit and vegetable, fat and carbohydrate intake, wellbeing, anxiety and excitement along with lifestyle covariates [T1; see equation (2)].

One-day lagged associations tested whether eating fruit and vegetable, fat or carbohydrate intake on 1 day (T0) correlated with changes in wellbeing, anxiety and excitement the next day (T1) while controlling for mood on the first day. Lifestyle variables (i.e., activity, sleep, social interactions) were entered as covariates and not lagged [see Equation (3)].

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TABLE 2 Association between diet and lifestyle factors and measures of wellbeing and mood, using multiple linear regression models.

DV	IV	Coefficient	95% CI	*P*
Wellbeing	Intercept	6.48	−1.10–14.07	0.093
	Fruit and vegetable	0.01	0.00–0.02	**0.013**
	Fat	0.01	−0.06–0.08	0.725
	Carbohydrates	0.03	−0.01–0.08	0.142
	Activity	0.02	−0.00–0.04	0.067
	Sleep	0.05	0.03–0.07	**<0.001**
	SI[a] quality	0.10	0.06–0.13	**<0.001**
	SI[a] quantity	0.00	−0.02–0.02	0.996
	Gender (male)	0.86	0.01–1.71	**0.048**
	R^2/R^2 adjusted	0.528/0.493		
Anxiety	Intercept	1.91	−0.42–4.24	0.107
	Fruit and vegetable	−0.00	−0.01–0.00	0.171
	Fat	0.01	−0.01–0.03	0.289
	Carbohydrates	0.01	−0.01–0.02	0.396
	Activity	0.00	−0.01–0.01	0.776
	Sleep	−0.00	−0.01–0.00	0.452
	SI[a] quality	−0.01	−0.02 to -0.00	**0.007**
	SI[a] quantity	0.01	−0.00–0.01	0.145
	Gender (male)	−0.45	−0.72 to -0.19	**0.001**
	R^2/R^2 adjusted	0.186/0.125		
Excitement	Intercept	1.52	−0.63–3.68	0.164
	Fruit and vegetable	−0.00	−0.00–0.00	0.999
	Fat	−0.00	−0.02–0.02	0.707
	Carbohydrates	0.00	−0.01–0.01	0.956
	Activity	0.01	−0.00–0.01	0.111
	Sleep	0.01	0.00–0.02	**0.012**
	SI[a] quality	0.01	−0.00–0.02	0.062
	SI[a] quantity	0.01	−0.00–0.01	0.096
	Gender (male)	0.14	−0.10–0.38	0.252
	R^2/R^2 adjusted	0.242/0.186		

[a]Social interaction.
All independent variables were entered simultaneously. The bold values mean $p < 0.05$.

Similarly, 2-day lagged analyses tested whether eating fruit and vegetables, carbohydrates, or dietary fats on 1 day (T0) were associated with wellbeing, anxiety or excitement 2 days later [T2; see Equation (4)]. Gender was dummy-coded.

$$(2)\ \text{DVT1} \sim \text{fruit \& vegetables T1} + \text{fat T1} + \text{carbohydrate T1} + \text{activity T1} + \text{sleep T1} + \text{quality of social interaction T1} + \text{quantity of social interaction T1} + \text{gender} + \text{DVT0} + (1 \mid \text{id})$$

$$(3)\ \text{DVT1} \sim \text{fruit \& vegetables T0} + \text{fatT0} + \text{carbohydrateT0} + \text{activity T1} + \text{sleep T1} + \text{quality of social interaction T1} + \text{quantity of social interaction T1} + \text{gender} + \text{DVT0} + (1 \mid \text{id})$$

$$(4)\ \text{DVT2} \sim \text{fruit \& vegetables T0} + \text{fatT0} + \text{carbohydrateT0} + \text{activity T2} + \text{sleep T2} + \text{quality of social interaction T2} + \text{quantity of social interaction T2} + \text{gender} + \text{DVT1} + (1 \mid \text{id})$$

Exploratory analyses

Exploratory associations between self-reported average fruit and vegetable, fat and carbohydrate intake, sleep, activity, social interaction quality and quantity and mental health questionnaires were tested with Pearson correlations. Significance levels were Bonferroni-corrected for multiple comparisons for each DV separately. Estimated marginal means analysis allowed us to test independent variable × gender effects on wellbeing and were carried out using the *emmeans* package (50). Mediation with covariates was conducted using the *MeMoBootR* package (48).

Preregistration

Preregistered hypotheses and analyses are available on the public data repository Open Science Framework (see text footnote 1). We had not preregistered analysis by gender initially, however, after a more in-depth literature analysis it became clear, that gender differences play a larger role than we had previously assumed (8, 19). Therefore, we included gender as a covariate in all models, and tested correlations between wellbeing and (a) fruit and vegetable intake; and (b) social interaction quality stratified by gender.

We intended to include baseline wellbeing as a covariate in the wellbeing model, and similarly, perceived stress (PSQ) and trait anxiety (STAI) as covariates in the anxiety weekly averaged models. However, after observing high correlation between these measures we decided not to include these to avoid biased coefficients (51). In the mixed-effects models we included their wellbeing, anxiety, or excitement levels of the previous day as a covariate following (13) to test associations with daily wellbeing, anxiety, and excitement.

Finally, we originally wanted to use difference scores between habitual and concurrent lifestyle behaviors as mediators. However, at the time of conducting the study, light lockdown had been re-instated for more than 2 weeks. We reasoned that habitual data would reflect lockdown habits rather

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than pre-lockdown behaviors. Therefore, we used concurrent data of lifestyle behaviors instead.

Results

Participants

A total of 135 individuals participated in the study. After data collection, we excluded participants with severe symptom severity on the BDI (> 30, N = 3) as well as participants who logged fewer than 4 days of food intake and mood diary (N = 15). This resulted in a total sample of 117 participants (women N = 45, men N = 72, other = 0). Prior to the study, a power analysis based on a small effect size (f = 0.15), alpha = 0.05, and power of 0.95, estimated a required sample size of 119. Our final sample of N = 117 would deem sufficient.

Averages of daily mood ratings and lifestyle factors are reported alongside baseline and trait questionnaire scores in Table 1. As shown in this table, in our sample women were significantly older than men, and had a lower BMI on average. Intake of kilocalories also differed between men and women

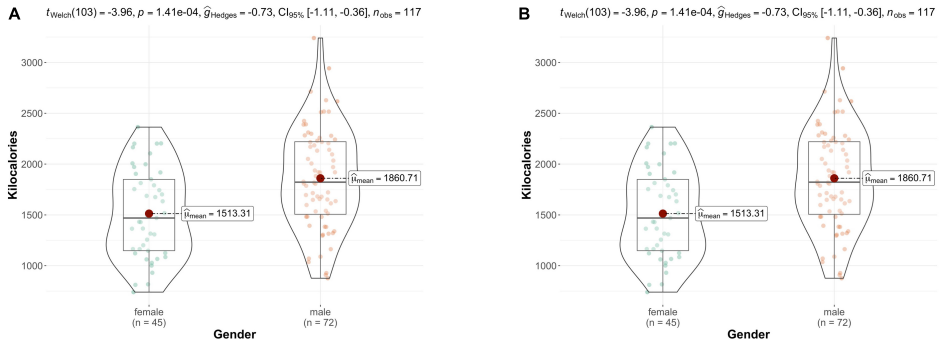

FIGURE 2
(A) Intake of kilocalories by gender; **(B)** energy adjusted fruit and vegetable intake by gender. Female participants consumed significantly more fruit and vegetables adjusted for total energy intake. Bars represent the interquartile range, with the median drawn in the middle. Whiskers depict the minimum and maximum values.

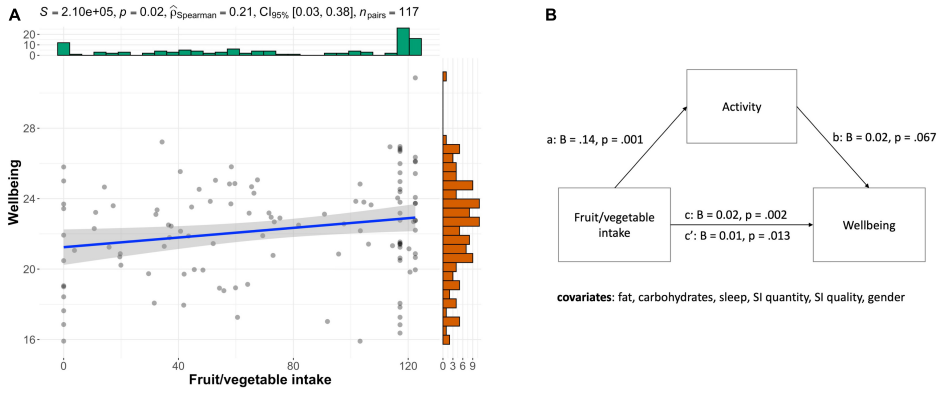

FIGURE 3
Fruit and vegetable intake affects wellbeing which is partially mediated by activity. **(A)** Scatterplot showing that fruit and vegetable intake correlates positively with wellbeing (rho = 0.21, p = 0.021). **(B)** Mediation model, illustrates that higher levels of fruit and vegetable intake were associated with more activity on average (*a*) and a higher level of wellbeing (*c*). Activity showed a non-significant positive trend for wellbeing (*b*). After accounting for the indirect effect, the direct effect remained significant, meaning fruit/veg intake contributes to wellbeing independently of activity (c').

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(Figure 2A), whereby men had a higher total energy intake and consumed more protein than women. However, women had a significantly higher intake of fruit and vegetables (Figure 2B).

Daily mood and lifestyle ratings differed insofar that women reported higher levels of anxiety but also rated their social interactions of a higher quality. Trait anxiety levels were also higher in women than in men. No other significant differences between men and women were found.

Weekly averages of daily data

We investigated whether wellbeing, anxiety and excitement was associated with averages of the diary data in inter-individual models. Based on the multiple regression models, and as shown in Table 2, we found that fruit and vegetable intake correlated with wellbeing (B = 0.01, CI = 0.00–0.02, $p = 0.013$) alongside sleep (B = 0.05, CI = 0.03–0.07, $p < 0.001$), social interaction quality (B = 0.10, CI = 0.06–0.13, $p < 0.001$) and male gender (B = 0.86, CI = 0.01–1.71, $p = 0.048$). Anxiety was significantly associated with social interaction quality (B = −0.01, CI = −0.02 to −0.00, $p = 0.007$) and male gender (B = −0.45, CI = −0.72 to −0.19, $p = 0.001$). Finally, excitement correlated with sleep quality (B = 0.01, CI = 0.00–0.02, $p = 0.012$).

Mediation analyses

Next, we tested if concurrent lifestyle (activity, sleep, social interactions) mediated the effect of food intake on wellbeing while controlling for all other lifestyle factors. To validate using a mediation model, we first tested if fruit and vegetable, fat and carbohydrate intake each regress onto wellbeing, which revealed that only fruit and vegetable intake significantly correlated with wellbeing ($B = 0.02$, SE = 0, $t = 3.20$, $p = 0.002$). Next, we tested whether the independent variable fruit and vegetable intake regressed onto the mediators (activity, sleep, social interactions). Fruit and vegetable intake correlated with activity ($B = 0.14$, SE = 0.04, $t = 3.35$, $p = 0.001$) but neither sleep ($B = -0.02$, SE = 0.041, $t = -0.51$, $p = 0.614$) nor quality of social interaction ($B = -0.00$, SE = 0.03, $t = -0.05$, $p = 0.960$). Thus, we ran a mediation model to test whether activity mediated the effect of fruit and vegetable intake on wellbeing (Figure 3). Indeed, this model revealed that the difference in activity partially mediated the direct effect of fruit and vegetable intake on wellbeing (c', $B = 0.01$, SE = 0.01, $t = 2.52$, $p = 0.013$) compared to the total effect (c, $B = 0.02$, SE = 0, $t = 3.20$, $p = 0.002$; bootstrapped indirect effect (B = 0.03, SE = 0, 95% CI −0.00–0.01).

Daily and lagged analyses

We also tested intra-individual associations between daily fruit and vegetable, fat and carbohydrate intake and changes in wellbeing using linear mixed-effects models controlling for wellbeing, anxiety, or excitement of the same day, respectively. The results for same-day analyses are shown in Table 3. Same-day wellbeing correlated with fruit and vegetable intake while controlling for same-day sleep, activity and quality, and quantity of social interactions and the previous day's wellbeing. Neither anxiety nor excitement were associated with diet, but by same-day lifestyle factors.

We also tested 1-day (Supplementary Table 1) and 2-day-lagged (Supplementary Table 2) associations of fruit and vegetable, fat and carbohydrate intake on wellbeing, anxiety, and excitement each controlling for same-day lifestyle factors revealing similar patterns. For 1-day lags none of the dietary components correlated with wellbeing, anxiety or excitement (all $p > 0.296$). Instead, daily wellbeing was significantly associated with lifestyle factors sleep, activity, social interaction quality, and the previous day's level of wellbeing (all $p = 0.001$ or < 0.001). Anxiety was correlated with sleep and quality of social interactions (all $p < 0.001$), the previous day's level of anxiety ($p = 0.002$) as well as male gender ($p = 0.029$). Finally, excitement was associated with sleep, activity, social interaction quality (all $p = 0.001$ or < 0.001), and the previous day's level of excitement ($p = 0.018$). Two-day lagged associations did not reveal any significant diet associations when accounting for lifestyle factors in the same model (all $p > 0.184$).

Exploratory analyses

We explored correlations between mental health questionnaires and individuals' average dietary and lifestyle behaviors. In Table 4 we report Pearson correlations between baseline mental health and wellbeing questionnaires (as dependent variables) and diet and lifestyle variables. We found that fat intake correlates positively with trait anxiety ($r = 0.30$, $p = 0.007$). In addition, self-rated sleep quality and social interaction quality significantly correlate with all dependent variables.

Association with the dietary inflammatory index

As inflammation is a possible mechanism by which diet affects mental wellbeing, we tested if a high Dietary Inflammatory Index (DII) is associated with lower wellbeing and higher levels of anxiety. DII score correlated significantly with averaged daily wellbeing ($r = -0.20$, $p = 0.027$, Figure 4A) but not with anxiety ($r = 0.17$, $p = 0.063$) or excitement ($r = -0.09$, $p = 0.332$).

Based on the mediation effect we found above, we also tested if average daily lifestyle (i.e., activity, sleep, social interactions) mediated the effect of an inflammatory diet on wellbeing. DII

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TABLE 3 Same-day associations between diet and lifestyle factors and measures of wellbeing and mood, using linear mixed-effects models.

DV	IV	Coefficient	95% CI	*P*
Wellbeing	Intercept	9.16	5.74–12.58	<**0.001**
	Fruit and vegetable	0.01	0.00–0.01	**0.002**
	Fat	0.01	−0.02–0.04	0.531
	Carbohydrates	0.01	−0.01–0.02	0.552
	Sleep	0.03	0.02–0.04	<**0.001**
	Activity	0.02	0.01–0.03	<**0.001**
	SI[a] quality	0.07	0.06–0.08	<**0.001**
	SI[a] quantity	0.01	0.00–0.03	**0.018**
	Previous day wellbeing	0.15	0.09–0.22	<**0.001**
	Gender (male)	0.56	−0.16–1.28	0.129
	Random effects			
	N_{id}	109		
	Observations	475		
	Marginal R^2/Cond. R^2	0.462/0.588		
Anxiety	Intercept	2.11	1.03–3.19	<**0.001**
	Fruit and vegetable	−0.00	−0.00–0.00	0.686
	Fat	0.00	−0.01–0.01	0.611
	Carbohydrates	0.01	−0.00–0.01	0.075
	Sleep	−0.01	−0.01 to -0.00	**0.001**
	Activity	−0.00	−0.00–0.00	0.445
	SI[a] quality	−0.01	−0.01 to −0.00	**0.001**
	SI[a] quantity	−0.00	−0.01 to −0.00	**0.044**
	Previous day anxiety	0.12	0.04–0.20	**0.004**
	Gender (male)	−0.29	−0.52 to -0.05	**0.019**
	Random effects			
	N_{id}	109		
	Observations	479		
	Marginal R^2/Cond. R^2	0.144/0.336		
Excitement	Intercept	1.21	0.14–2.27	**0.027**
	Fruit and vegetable	0.00	−0.00–0.00	0.964
	Fat	0.00	−0.01–0.01	0.756
	Carbohydrates	−0.00	−0.01–0.00	0.560
	Sleep	0.01	0.00–0.01	**0.001**
	Activity	0.01	0.00–0.01	**0.001**
	SI[a] quality	0.01	0.01–0.02	<**0.001**
	SI[a] quantity	0.00	−0.00–0.01	0.119
	Previous day excitement	0.08	−0.00–0.16	0.055
	Gender (female)	0.18	−0.05–0.41	0.129
	Random effects			
	N_{id}	109		
	Observations	477		
	Marginal R^2/Cond. R^2	0.241/0.407		

[a]Social interaction.
All independent variables were entered simultaneously. The bold values mean $p < 0.05$.

negatively correlated with wellbeing (B = −0.20, SE = 0.10, t = −2.00, p = 0.047). As for possible mediators, DII negatively correlated with activity (B = −2.58, SE = 0.86, t = −3.00, p = 0.003) but neither sleep (B = −0.37, SE = 0.84, t = −0.44, p = 0.658) nor social interaction quality (B = −0.15, SE = 0.62, t = −0.23, p = 0.815). Therefore, we tested for a mediation of activity only. We found that activity fully mediated the direct effect (c') of the dietary inflammatory score on wellbeing (B = −0.14, SE = 0.11, t = −1.32, p = 0.191) compared to the total effect (c, B = −0.21, SE = 0.10, t = −2.00, p = 0.047; bootstrapped

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TABLE 4 Pearson correlations between baseline mental health and wellbeing questionnaires and diet and lifestyle outcomes.

	Wellbeing	Anxiety	Depressive symptoms	Perceived stress
Fruit and vegetable	0.21	−0.10	−0.16	−0.12
Fat	−0.19	**0.30****	0.13	0.22
Carbohydrates	0.20	−0.24	−0.18	−0.19
Sleep	**0.39*****	**−0.34****	**−0.36*****	**−0.37*****
Activity	0.23	−0.20	**−0.27***	−0.21
Social interaction quality	**0.43*****	**−0.32****	**−0.39*****	**−0.29***
Social interaction quantity	0.19	−0.03	−0.17	−0.06

P-value adjustment method: Bonferroni; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. Significance levels were corrected for multiple comparisons for each DV separately. The bold values mean $p < 0.05$.

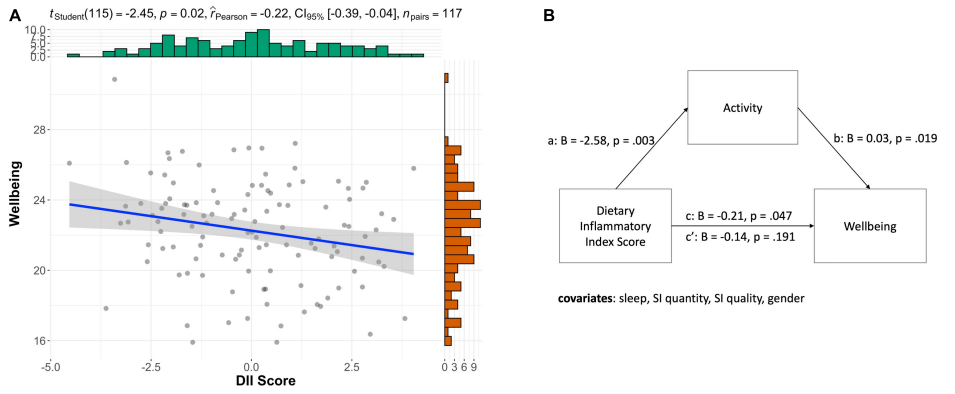

FIGURE 4
Dietary inflammatory index, wellbeing, and activity. **(A)** Negative correlation between DII and average wellbeing ($r = 0.22$, $p = 0.016$). **(B)** Mediation model illustrating that a more inflammatory diet was associated with being less active (*a*) and reporting lower levels of wellbeing (*c*). While more activity was also associated with higher wellbeing (*b*).

indirect effect ($B = -0.07$, SE = 0.04, 95% CI −0.15 to 0.00) as shown in Figure 4B.

Gender-specific effects

Given that female participants consumed significantly more fruits and vegetables compared to men [$M_{female} = 91.96$ (35.17), $M_{male} = 62.48$ (44.89), $p = 0.009$], we explored if the strength of the association between fruit and vegetable intake and wellbeing differed depending on gender. However, as shown in Figure 5, an estimation of the marginal means of linear trends did not show that the interaction between gender and fruit/vegetable intake was significantly different ($B = -0.01$, $p = 0.409$).

Given that age and BMI significantly differed between male and female participants (see Table 1), we wondered if these variables could account for the gender effects we found. While fruit and vegetable intake correlated negatively with BMI ($r = -0.18$, $p = 0.048$), wellbeing did not ($r = -0.07$, $p = 0.440$). However, age did not correlate with either wellbeing ($r = 0.05$, $p = 0.575$) or fruit and vegetable intake ($r = 0.13$, $p = 0.166$).

The effect of Dietary Inflammatory Index on wellbeing was also independent of gender ($B = -0.10$, $p = 0.732$). Furthermore, we were curious as to whether gender differently interacted with social interaction quality and wellbeing. This was not the case ($B = 0.05$, $p = 0.126$); for both genders, social interaction quality positively affected wellbeing (for women: $B = 0.15$, $p < 0.001$; for men: $B = 0.10$, $p < 0.001$). Likewise, sleep was positively associated with wellbeing in both genders (overall contrast: $B = 0.07$, $p = 0.007$, for women: $B = 0.12$, $p < 0.001$; for men: $B = 0.05$, $p = 0.003$).

Discussion

This preregistered study investigated how dietary intake affected mood and wellbeing alongside lifestyle factors during COVID-19-lockdown. Previous studies showed that dietary

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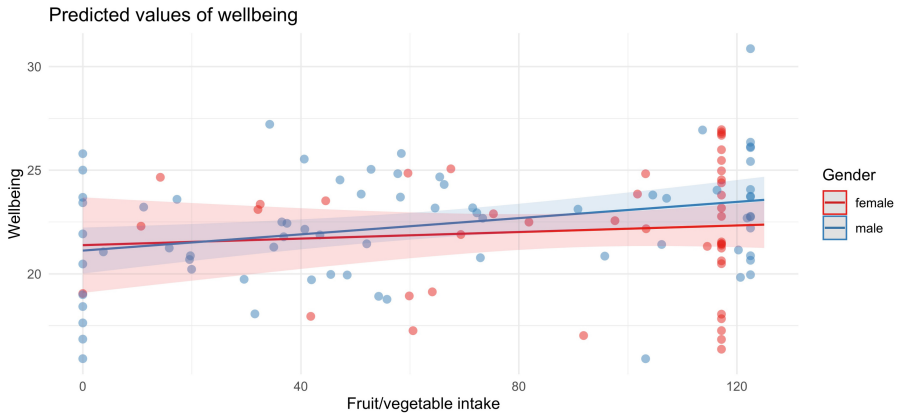

FIGURE 5
Both men (blue) and women (red) showed a positive association between fruit and vegetable intake and wellbeing.

components (7, 13, 14), exercise and sleep impacted on mental health and wellbeing (4). We were also interested in social interaction as a contributor to wellbeing (29), since social distancing measures were so prominent during lockdowns.

We hypothesized that food intake was associated with (1) wellbeing; (2) anxiety; and (3) excitement and tested between- and within-person relationships while controlling for concurrent lifestyle factors. Both in our regression models, as well as mediation analysis, we observed that fruit and vegetable intake correlated with wellbeing, while this was partially mediated by physical activity.

Diet and lifestyle in the context of COVID-19-lockdown

The pandemic context brought about changes in diet, sleep, and activity (52), which brought about increased negative mood (52–55) and lower wellbeing (1). Lower dietary quality was associated with poor mood and may have been used to regulate emotions (55). The present findings complement this by providing evidence that inversely, consuming healthier foods, i.e., fruit and vegetable, were linked with more wellbeing. Work by Cecchetto and colleagues' investigated whether social factors (amongst others) contributed to dysfunctional eating habits during the pandemic (36). However, a more holistic approach of lifestyle factors that include physical activity, sleep, dietary intake and social interaction to investigate their joint effect on wellbeing, anxiety and excitement had thus far been lacking.

Undergoing lockdown may have undermined the impact of diet on mood when accounting for other healthful behaviors. For example, mood affects the likelihood of making healthy food choices mediated by physical activity (56). The authors suggest that people engage in healthy *lifestyles* rather than isolated health behaviors, i.e., being physically active goes together with making healthier dietary choices (56). Our data support this notion; high intakes of fruit and vegetable as well as physical activity were associated with increased levels of wellbeing.

Additionally, other lifestyle factors may have gained importance during this period. Highly active people experienced significant declines in quality of sleep and wellbeing during lockdown as compared to sedentary individuals (2). Furthermore, dramatic declines in physical activity, especially walking, were recorded due to lockdown restrictions and increased home-office hours or job termination in this period (57). Being active outdoors compared to indoors may contribute further to mental wellbeing in addition to the exercise itself (58). The more time spent outdoors in daylight lowered the risk of depression, low mood and added to happiness (59). Thus, lockdown restrictions may have magnified beneficial effects of physical activity during lockdown, and even more so when activity happened outdoors.

Finally, social interactions were greatly affected by social distancing measures. For example, social media use increased during the pandemic (60) and was linked to poor mental health in a large cross-country sample (61), and increased the odds of experiencing anxiety in a Chinese (62) and American sample (60). While greater social connectedness was associated with less perceived stress during the pandemic (63). In line with the existing literature, we found that the quality but not quantity of social interactions correlated with mood and wellbeing in almost all analyses, echoing previous findings (64). To our knowledge, social interactions have not yet been considered in models alongside diet, sleep, and activity. Our findings

suggest that during lockdown the quality of social interactions plays a key role when examining the relationship between diet, wellbeing, and mood.

Evaluating dietary intake

Dietary intake can be analyzed in many different ways. Here we focused on specific dietary components. Fat, carbohydrates, and fruit and vegetable intake had been identified in the literature to play a key role in mood and wellbeing (13, 14, 65). Our findings supported the role of fruit and vegetable intake in concurrent wellbeing. Furthermore, we found an association between trait anxiety and fat intake, whereby higher fat intake correlated with greater state anxiety. However, we did not find that total fat intake correlated with daily anxiety levels when controlling for other lifestyle factors.

Additionally, we calculated the dietary inflammatory index—a well-established measure of a diet's inflammatory potential (16). We found that DII score correlated negatively with average wellbeing but not with anxiety or excitement. DII score has been found to correlate with wellbeing before (66). We also found that the effect of DII on wellbeing was fully mediated by activity.

We examined whether dietary intake was associated with wellbeing, anxiety, and excitement. However, vice versa, it is an interesting question whether negative mood and mental health issues can drive low-quality food intake. Neither longitudinal (67) nor short-term evidence, 1- or 2-day lagged associations (13, 14) support this idea. However, a recent study conducted during COVID-19-lockdown found that mood states were linked to the intake of fruit, vegetables, and fish, which were partially mediated by physical exercise load (56). The authors suggested that some participants may have actively changed their exercise and food intake behavior to deal with the anticipated challenges on mental health during lockdown (56). Importantly, these authors included exercise as a lifestyle factor to investigate the relationship between mood and diet. In sum, the differences between studies may be due to the unusual circumstances of the pandemic as well as the mediating factor of physical exercise, which was affected by pandemic restrictions (27, 57). Finally, Amatori et al. did not report testing the reverse direction, i.e., whether dietary intake was correlated with mood states (56).

Gender-specific effects

Here we found gender differences in food intake, anxiety levels, and quality of social interaction. In particular, women consumed more fruit and vegetables but fewer calories from protein than men. This is in line with previous work demonstrating gender differences in dietary intake (68–70). For instance, women across 23 countries showed greater beliefs in the importance of healthy eating as evident by higher intake of fruit and fiber-rich foods (70). In this study, women reported higher baseline and concurrent anxiety levels than men in this study, consistent with previous findings (71). But we did not find that higher fruit and vegetable intake was associated with lower anxiety ratings, contrary to what has been reported elsewhere (8). Eating more fruit and vegetables also did not affect wellbeing to a greater extent than men. It is currently unclear why women's mood did not benefit from fruit and vegetable intake more so than men despite higher intake, or why anxiety levels were unaffected by higher fruit and vegetable intake. Thus, more research is needed to better understand mechanistic links between diet, body, brain, and gender interactions.

Strengths and limitations

A few limitations need to be considered. First, due to the acute nature of the pandemic, we lack a baseline dietary assessment, and cannot make claims whether dietary intake has changed in response to the lockdown. Second, as with any self-report study, these measures underlie self-reporting biases. For example, self-reported caloric intake is likely underreported. Underreporting is a common problem in self-reported dietary data (72). Note that we also chose to exclude individuals with mental health diagnoses and severe depressive symptoms, therefore our findings cannot be generalized to subclinical and clinical populations.

Strengths of this study include the use of preregistration of hypotheses and analyses before data collection. Considering that dietary intake alongside multiple lifestyle factors and social aspects is still understudied, highlights the need for a holistic approach to assess lifestyle with mood and mental health outcomes. Furthermore, we were able to collect a rich data set by assessing baseline parameters of mental health and lifestyle followed by a 7-day diary of food intake. Using such a food diary, rather than a 24-hr recall, alongside concurrent mood and lifestyle factors allowed us to explore both inter- and intra-individual fluctuations of these variables. The findings of this study are limited to a relatively young German population, and further research would be needed to determine if the same effects can be found for different age groups and specific health groups. An interesting avenue for future studies would be to investigate whether the dynamic between mood, diet, lifestyle, and social interactions still holds beyond the acute lockdown situation observed in this study, and whether this extends to different individuals such as clinical populations.

Conclusion

Our results showed that, on average, fruit and vegetable intake contributed to wellbeing alongside sleep and social

interaction quality. Examining day-to-day associations showed that fruit and vegetable intake on the same day promoted wellbeing, while this was not the case for the next day or second day time lags. Instead, sleep, activity, and social interactions were associated with wellbeing in the context of lockdown during the COVID-19 pandemic. Importantly, associations between fruit and vegetable intake were partially mediated by physical activity. These findings highlight the need for an integrated way of assessing lifestyle factors and gender in future studies. As pandemics are thought to appear more frequently due to diminishing biodiversity (73), strategies to protect mental health and wellbeing become more important than ever, especially because access to mental health care remains limited for many. Therefore, reducing the risk for adverse psychological effects *via* lifestyle behaviors such as diet, activity, and sleep remains a promising strategy [for a meta-review on lifestyle psychiatry see Firth et al. (4)].

In conclusion, a combination of physical activity, good sleep, and daily high-quality social interactions as well as a diet rich in fruit and vegetables and a low inflammatory potential (i.e., diets high in minerals and vitamins, such as fruit and vegetables, but low in saturated fats) appears to promote better mood and wellbeing in stressful circumstances such as a lockdown during a global pandemic. Our research result offers a novel perspective of dietary and lifestyle recommendations that can be provided in times of high uncertainty, such as pandemic situation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Humboldt University of Berlin. The patients/participants provided their written informed consent to participate in this study.

Author contributions

A-KM and SP: conceptualization and project administration. A-KM: investigation, visualization, and writing—original draft preparation. A-KM, AL, and SP: methodology and formal analysis. A-KM, AL, DT, and SP: writing—review and editing. AL and SP: supervision. SP: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.993180/full#supplementary-material

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Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

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