Aus der Klinik für Neurologie
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Dissertation

Psychophysiological investigations on eating behaviour

Psychophysiologische Untersuchungen zum Essverhalten

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Science cannot solve the ultimate mystery of nature. And that is because, in the last analysis, we ourselves are part of nature and therefore part of the mystery that we are trying to solve.
— Max Planck

Eat what you want to sustain.
— Ursula Hudson

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List of Abbreviations

ASV	amplicon sequence variants
BMI	body-mass-index
CO_2eq	CO_2 equivalents
DMN	default mode network
DNA	deoxyribonucleic acid
FFQ	food frequency questionnaire
fMRI	functional magnetic resonance imaging
GHG	greenhouse gas emissions
GLP-1	glucagon-like peptide-1
LC–MS	liquid chromatography-mass spectrometry
MPRAGE	magnetization prepared rapid gradient echo
MR	magnetic resonance
MRI	magnetic resonance imaging
NAc	nucleus accumbens
NCD	non-communicable disease
PYY	peptide tyrosine-tyrosine
RCT	randomised controlled trial
rRNA	ribosomal ribonucleic acid
rsfMRI	resting-state functional magnetic resonance imaging
RYGB	Roux-en-Y gastric bypass
SCFA	short-chain fatty acid
VTA	ventral tegmental area

Abstract (English)

Introduction. Malnutrition is a global challenge with mortality rates caused by obesity surpassing those of undernutrition. Excessive and low quality food intake detrimentally impacts human and planetary health likewise. In contrast, high fiber diets are beneficial for host metabolism and for the environment. Yet, diet-related behaviour change remains challenging, both on the systemic and the individual level. It remains largely unclear how high fiber diets act on the host in detail, to what extent gut-brain communication is involved, and by which mechanisms eating behaviour may be modulated and maintained. To this end, I investigated underlying mechanisms of eating related psychophysiological markers in humans in three studies.

Methods. I examined changes in brain connectivity networks as proxies for reward and self-reflective processing induced by severe weight loss through bariatric surgery in a clinical sample of obese compared to waiting list control patients (n = 48, **Study 1**). I combined data from two independent cross-sectional studies: overweight adults (n = 27) and post-bariatric surgery groups with age-, sex- and BMI-matched control groups (n = 40). Primary measures of interest were eating behaviour, microbial genera abundance, and fiber intake or weight loss success, respectively, next to short-chain fatty acids in feces and serum (**Study 2**). I analysed data from the LIFE-Adult cohort study (n = 8,943) relating habitual diet to weight status, depressive symptoms and personality traits (**Study 3**). Additionally, I conducted a within-subject cross-over dietary intervention study (n = 60) including brain imaging, cognitive tasks and biomarkers, and a series of large-scale online studies (n = 16,379).

Results. In **Study 1**, we found no significant post-surgery changes in brain connectivity in confirmatory analyses. Exploratory results showed increased connectivity between the reward network to medial posterior frontal regions relating to treatment success. In **Study 2**, eating behaviour linked differentially to two groups of microbial genera. Indeed, those linked to unhealthier eating were found to be informative of treatment success post-bariatric surgery, in terms of higher weight loss and improved eating traits. In **Study 3**, less frequent animal-based food intake was significantly related to lower BMI and to lower extraversion, not to depressive symptoms.

Conclusion. These results propose a complex cross-talk between eating behaviour and psychophysiological markers and i) indicate a link between therapy-induced weight loss and reward-related brain processes, ii) provide first evidence for links between eating behaviour and gut microbiota and iii) replicate known associations of high fiber diets and weight status, as well as add new insights on diet-related differences in personality traits. Future interventional studies need to investigate causality of gut-brain communication and its mechanistic pathways related to fiber.

Abstract (German)

Einleitung. Mangelernährung ist ein globales Problem, wobei die durch Adipositas verursachte Sterblichkeitsrate die der Unterernährung übersteigt. Eine übermäßige, minderwertige Ernährung wirkt sich gleichermaßen negativ auf die menschliche und planetare Gesundheit aus. Im Gegensatz dazu ist eine ballaststoffreiche Ernährung vorteilhaft für den Stoffwechsel und die Umwelt. Das Ernährungsverhalten zu verändern, bleibt jedoch eine Herausforderung, sowohl auf systemischer als auch auf individueller Ebene. Es ist weitestgehend unklar, wie eine ballaststoffreiche Ernährung auf den Wirt wirkt, inwieweit Darm-Hirn-Kommunikation beteiligt ist und durch welche Mechanismen das Essverhalten moduliert und beibehalten werden kann.

Methoden. Ich untersuchte Veränderungen von Gehirnkonnektivität, die mit Belohnung und Selbst-Reflexion assoziiert sind, nach bariatrischer Operation in einer klinischen Stichprobe im Vergleich zu Wartelisten-Patient:innen (n = 48) (**Studie 1**). In zwei unabhängigen Querschnittsstudien mit übergewichtigen Erwachsenen (n = 27) und solchen nach bariatrischer Operation sowie Kontrollgruppen (n = 40), betrachtete ich Essverhalten, die Abundanz mikrobieller Gattungen und Ballaststoffzufuhr bzw. therapeutischen Erfolg, sowie kurzkettige Fettsäuren in Feces und Serum (**Studie 2**). Ich analysierte den Zusammenhang zwischen Ernährung mit Gewicht, Depressivität und Persönlichkeit (n = 8,943, **Studie 3**). Auch führte ich eine randomisierte Ernährungsintervention (n = 60) mit Bildgebung des Gehirns, kognitiven Aufgaben und Biomarkern, sowie eine Serie von Online-Studien (n = 16,379) durch.

Ergebnisse. In **Studie 1** wiesen konfirmative Analysen auf keine signifikanten Veränderungen der Gehirnkonnektivität nach bariatrischer Chirurgie hin. Explorative Ergebnisse zeigten eine erhöhte Konnektivität zwischen dem Belohnungsnetzwerk und einer medial-posterioren frontalen Region in Verbindung mit dem Therapieerfolg. In **Studie 2** war Essverhalten unterschiedlich mit zwei Gruppen von Bakterien verbunden. Diejenigen, die mit ungesundem Essen in Verbindung standen, waren ebenso mit dem Therapieerfolg nach bariatrischer Operation assoziiert. In **Studie 3** stand die seltenere Aufnahme von tierischen Lebensmitteln in signifikantem Zusammenhang mit einem niedrigeren BMI und geringerer Extraversion, nicht aber mit Depressivität.

Schlussfolgerungen. Die Ergebnisse zeigen ein komplexes Zusammenspiel zwischen Essverhalten und psychophysiologischen Markern und i) weisen auf einen Zusammenhang zwischen therapiebedingter Gewichtsabnahme und belohnungsbezogenen Gehirnprozessen hin, ii) liefern erste Belege für Zusammenhänge zwischen Essverhalten und Darmmikrobiota und iii) replizieren Assoziationen zwischen ballaststoffreicher Ernährung und Gewicht, und bringen neue Erkenntnisse über ernährungsassoziierte Persönlichkeitsunterschiede. Interventionsstudien sollten die Kausalität der Darm-Hirn-Kommunikation und ihre mechanistischen Wege im Zusammenhang mit Ballaststoffen untersuchen.

1 Introduction

1.1 Facing a major health and climate crisis

Two of humanity's major challenges, malnutrition (over- and undernutrition) and the climate crisis, are highly intertwined. In fact, agricultural systems are the problem and solution at the same time to be focussed on to improve health and environmental impact of human food intake (**Figure 1**). Over- and undernutrition likewise are global epidemics, with currently higher prevalence and death rates caused by obesity and overweight than by underweight (WHO, 2021). Non-communicable diseases (NCD) often root in overconsumption of unhealthy foods, including red and processed meat, and sedentary lifestyles, leading to cardiovascular diseases, diabetes or cancer. The top three leading causes of death globally are caused by NCDs, namely ischemic heart disease, stroke and chronic obstructive pulmonary disease (WHO, 2020). Indeed, excess food intake has been translated to metabolic food waste making up 2% of total greenhouse gas emissions (GHG) of a representative country (Sundin et al. 2021).

Certainly, diets are a major lever for reducing human ecological impact due to their high climate footprint. Meta-analyses mainly based on field data show that food systems are responsible for 25-30% of anthropogenic GHG, 50% of habitable land use, 70% of freshwater use, 78% of ocean and freshwater eutrophication and the massive reduction in biodiversity (Poore and Nemecek 2018; Bar-On, Phillips, and Milo 2018). In particular, animal-derived foods contribute to these numbers: livestock value chains account for approximately 14.5% of global anthropogenic GHG (Gerber et al. 2013), 22% of the total groundwater footprint (Hoekstra and Mekonnen 2012) and 38% of global land use (FAO, 2003). Indeed, dairy products like cheese, included in lacto-vegetarian diets, have high impacts on all dimensions, with impacts second to beef (Poore and Nemecek 2018).

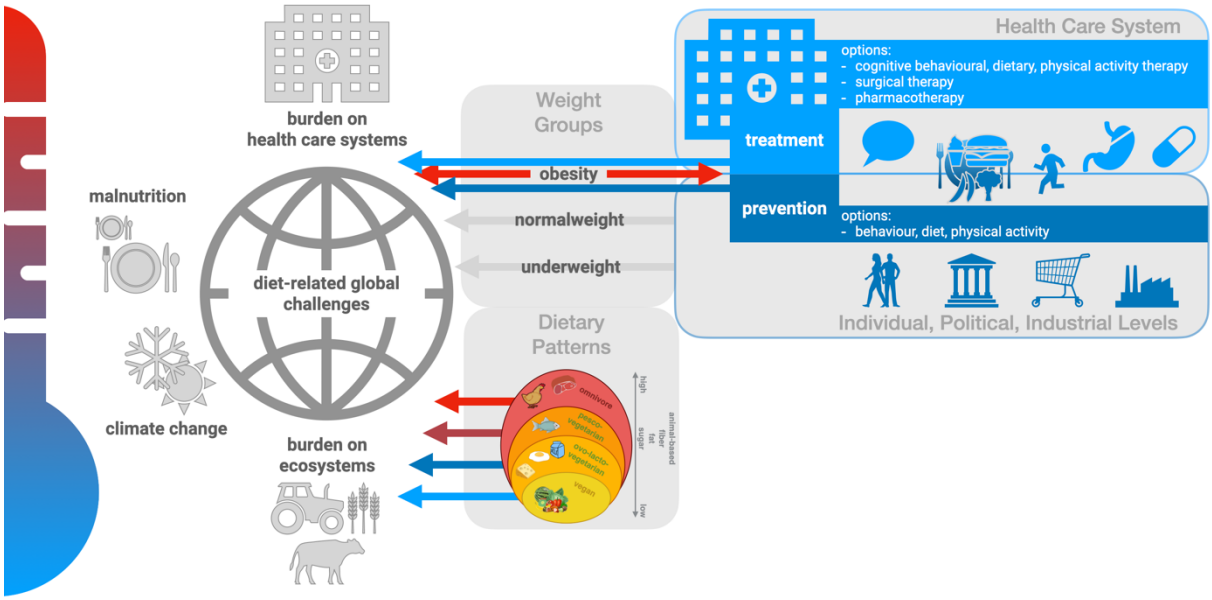

Figure 1: The global syndemic of malnutrition and climate change and its relation to weight groups and dietary patterns. Diet-related global challenges and how obesity treatment and prevention may counteract those with a focus on countries with a Western diet. Red colours represent warming/acceleration of the global challenges, whereas blue colours represent cooling/deceleration of those. Brighter colours depict stronger associations, and darker colours depict less strong associations. Note, that normal-weight and underweight, while globally important, were conceptually left out for simplification. Icons and have been taken from Keynote Library and the diagram depicting "Dietary Patterns" adapted from Medawar et al. (2019).

1.2 Obesity treatment options and weight management

Providing and improving efficacy of obesity-related treatment is a major task of health care systems worldwide and amounts to 20% of national health care costs in the United States and 11% in Germany (*The Heavy Burden of Obesity* 2019). Treatment options for obesity depend on severity of disease, personal risk factors and co-morbidities, and span from lifestyle adaptions targeting diet and physical activity, behavioural change, weight management programs, pharmacotherapy, weight-loss devices (e.g. intraoral jaw lock) to bariatric surgery. Although efficacy measured in weight loss is moderate to good, long-term weight maintenance remains a challenge (Hall and Kahan 2018). Lifestyle changes are the least invasive treatment, yet efficacy is moderate only (4-6 kg weight loss 1-2 years post-treatment) (Wirth, Wabitsch, and Hauner 2014). For instance, dietary counselling, primarily focusses on reducing energy quantity (by at least 500 kcal/day) and density and secondarily on the intake of five portions of fruit, vegetables and pulses a day. Fresh plant-based ingredients are high in fiber, which has been associated not only with multiple health benefits but also with improved satiety. Yet, recommended intake levels are mostly not met in the general population. Compared to conservative treatments, surgical interventions are more effective (20-40 kg weight loss 1-2 years post-treatment) in reducing body fat and mortality risk. Yet, they are highly invasive and considered a "last resort" treatment option and recommended for morbidly obese (body-mass-index (BMI) ≥ 40kg/m^2) or obese individuals (BMI > 30 and < 40 kg/m^2) with co-morbidities such as type 2 diabetes (Wirth, Wabitsch, and Hauner 2014; Dietrich et al. 2018). Most common and effective procedures are Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG), which both lead to a reduction in stomach volume and thereby to lower food intake. Indeed, post-surgery therapy entails lifelong nutritional supplementation, commonly gastrointestinal medication and interdisciplinary medical evaluation. In Germany, treatment options follow a set of guidelines and are administered according to responsiveness of treatment progress from least to most invasive (AWMF 050-001 S3-Leitlinie "Adipositas – Prävention und Therapie"[1]).

While efficacy of surgical therapy has shown to be high, non-invasive conservative treatments remain improvable. In particular, the latter could aid patients with non-severe obesity and the prevention of overweight and obesity with the co-benefits of lower invasiveness and lower or no need for lifelong behavioural and medical adaptions by the patient.

1.3 Transitioning towards high-fiber plant-based diets

One approach to addressing the two-fold problem of malnutrition, in particular overnutrition, and the climate crisis is adopting more sustainable diets, comprised of nutritious whole-food plant-based foods.

Firstly, mostly plant-based whole-grain diets, characterized by high fiber content, have been linked to human and planetary health (M. A. Clark et al. 2019). Indeed, a planetary health diet high in plant-based and restricted in animal-based ingredients has been proposed to benefit both human and environmental health within planetary boundaries (Willett et al. 2019). Fiber or nondigestible carbohydrates, most abundant in whole-grain, vegetables, legumes, potatoes and fruits, were found to relate to lower body weight and other metabolic benefits with disease outcome improvements of up to 30% regarding all-cause and cardiovascular-related mortality, coronary heart disease, stroke incidence and type 2 diabetes (systematic review in 185 prospective studies and 58 clinical trials (Reynolds et al. 2019)). Effects were highest for daily fiber intakes between 25 g and 29 g and complementary for fiber and whole grains.

[1] Note, that the guideline originating from April 2014 has expired in April 2019 and has not yet been revised. An updated guideline on surgical therapy has been released (AWMF 088-001 S3-Leitlinie 2018).

Secondly, complete or partial avoidance of animal products provides significant environmental benefits: reduction of 50-80% of anthropogenic GHG and land use requirements associated with individual diet (Aleksandrowicz et al. 2016; Hallström, Carlsson-Kanyama, and Börjesson 2015), approximately 50% of individual diet-associated water use (Aleksandrowicz et al. 2016), between 14-21% of global water use (Jalava et al. 2014), and a significant reduction in the N_2 footprint (Eshel et al. 2014) as systematic reviews assessing various sustainable diet patterns and dietary scenarios show. Simulations show that resource use of 1 kg of beef compared to a plant-based alternative is 10x higher for land use, 30x higher for GHG and about 17x higher for N_2 (Eshel et al. 2014).
Despite knowledge about environmental and health benefits of high fiber diets, adapting diet remains difficult due to required change of systemic and individual behaviour. Indeed, to realize sustainable diets globally, on the one hand, food systems need to transform substantially by restructuring agricultural production whilst considering socioeconomical factors and equity (Béné et al. 2020) and by establishing enabling environments, thereby tackling malnutrition in all forms similarly (Hawkes et al. 2020). And on the other hand, interventions aiming to change health behaviours need to be designed to facilitate behavioural adaptations on the individual level, which in general have shown to be small in effect, yet effective nonetheless (Conner and Norman 2017). In particular, motivation and reward systems play an important role in health-related behaviour change (Michaelsen and Esch 2021). Indeed, interventions related to weight management seem to be able to decrease liking and wanting for high-caloric food (Oustric et al. 2018), although mechanistically left unexplained.
Transitioning towards more sustainable diets, by increasing the ratio of plant-based to animal-based foods, by reducing climate-unhealthy foods like processed meat and dairy products and by replacing those with climate-healthy foods like fiber sources, may therefore serve as a putative public health strategy to reduce obesity prevalence.
Yet, the mechanistic understanding of the interplay of diet-brain-behaviour, in particular the effects of plant-based diets on the body, remain understudied. In particular, evidence on the underlying mechanisms related to sustainable healthy diets, including host metabolism and gut-brain communication, long-term maintenance of dietary goals, factors influencing food decision-making and the valuation of food items, remains largely unknown. Elucidating psychophysiological factors related to eating behaviour with regard to sustainable diets could serve as an important cornerstone for facilitating a transition towards those.
Next, three mechanisms of interest related to eating behaviour will be outlined, which will be investigated in three publications summarized in this dissertation.

1.4 Mechanisms I: Reward sensitivity, food decision-making, hedonic and homeostatic control

In order to understand, how food decisions are made in general and for specific eating patterns, the underlying brain mechanisms and pathways will be summarized here.
The gut-brain axis is an interdependent system, with two main neural networks that may be modulated by the gut, namely the hedonic and the homeostatic control systems. While homeostatic regulation of appetite is generated by real or perceived nutrient needs, hedonic control is generated by other than nutrient needs, such as subjective value of food items (Berthoud, Münzberg, and Morrison 2017). The intrinsic value of a food item consists of the integration of many of its constituents, i.e. exteroceptive sensory and gustatory signals and encoded reward value, which is thought to be processed in the ventromedial prefrontal cortex, regarded as the brain's valuation hub (Bartra, McGuire, and Kable 2013). Indeed, three dissociable phenomena of reward, i.e. wanting, liking and learning, can be mapped to distinct

neurobiological mechanisms and brain structures, that are subparts of the nucleus accumbens (NAc) (Berridge, Robinson, and Aldridge 2009). Moreover, interoceptive signalling via emotion regulatory processes might further determine the properties of food items, for instance by adding an emotionally comforting and rewarding value as in the case of 'comfort foods' (Weltens, Zhao, and Van Oudenhove 2014). Food decision-making relies on a complexity of cognitive processes leading up to an action, and next to valuation, self-regulatory mechanisms processed in the dorsolateral prefrontal cortex are involved (Hare, Malmaud, and Rangel 2011). Further, gut signals might be modulators of human decision-making communicating bottom-up to the brain (Plassmann et al. 2021), in particular acting on hedonic regulation in the ventral tegmental area (VTA) and NAc and on homeostatic regulation in the hypothalamus (García-Cabrerizo et al. 2021).

Obesity on the one hand and restrictive diets on the other hand, are oftentimes discussed to be associated with imbalances in food decision-making, i.e. overeating, uncontrolled eating or restrained eating (Garcia-Garcia et al. 2021; Brytek-Matera 2020). When regulatory mechanisms are out of balance, overeating and over-compensatory mechanisms in food intake can lead to obesity and eating disorders. Specifically, unintended overeating and uncontrollable food craving leading to food intake beyond homeostatic needs has been conceptualized as food addiction behaviour by some (Gupta, Osadchiy, and Mayer 2020; Volkow, Wise, and Baler 2017), but regarded as too preliminary by others (Ziauddeen and Fletcher 2013). Sensitivity to rewards, in particular to foods, on the neural level can be measured recording brain activity while seeing food cues (task functional magnetic resonance imaging (fMRI)) or recording task-independent resting-state fMRI (rsfMRI). In particular, cue reactivity and reward signalling for palatable foods is assumed to be hyper- or hyposensitive in obesity, yet evidence is mixed and highlights the importance of confounding factors such as age (Kenny 2011; Morys, García-García, and Dagher 2020). Resting-state connectivity reflects temporal coherence of brain areas and is grouped into networks that are based on coherent activation and linked to associated functions, e.g. the default mode network (DMN) or the reward network. Functional connectivity in individuals with or without food addiction symptomatic has been shown to be distinct, in particular higher within-reward network connectivity correlated with higher food craving scores (Ravichandran et al. 2021). Potentially, obesity-related reward network differences may be reversable with bariatric surgery (Schmidt et al. 2021; Hankir et al. 2020), yet studies including large samples with adequate BMI-matched control groups are missing.

In particular, for restrictive diets, such as plant-based diets, it remains unclear, if fiber or other dietary constituents might act differently on homeostatic or reward-related brain pathways.

1.5 Mechanisms II: Dietary fiber and satiety and the gut-brain axis

Evidence for satiety-inducing effects of dietary fiber and its relevance in establishing and maintaining healthy host and gut metabolism will be reviewed here, yet mechanisms of action are largely unknown.

As a conservative treatment and preventive strategy for obesity and other NCDs, a healthy balanced diet is recommended for the general population and should consist of a daily fiber intake of 25-35 g including whole-grain foods (Reynolds et al. 2019). Indeed, meta-analytical evidence of randomised trials show beneficial metabolic effects of high compared to low fiber intake on bodyweight (-0.4 kg), glucose metabolism (-0.4 % glycated haemoglobin A_{1c}), lipid markers (-0.2 mmol/L in total cholesterol) and systolic blood pressure (-1.3 mmHg) (Reynolds et al. 2019).

Non-digestible types of fiber, such as fructooligosaccharides, inulins, galactans, resistant starch and others, serve as a source of energy for gut bacteria and are called prebiotics. Upon ingestion, prebiotics surpass the upper parts of the gastrointestinal tract and are processed in the colon by bacterial fermentation into short-chain fatty acids (SCFA) (Alexander et al. 2019). SCFA provide energy for colonic cells and might act as signalling molecules through different pathways including endocrine and vagal pathways, lastly modulating brain response to food intake and appetite (Dalile et al. 2019; Han et al. 2021): the endocrine pathway involves the release of glucagon-like peptide-1 (GLP-1) and peptide tyrosine-tyrosine (PYY) by enterochromaffin cells in the large intestine, both anorectic hormones, that lead to bottom-up signalling of reduced appetite. The vagal pathway includes appetite-regulative signalling, e.g. via orexigenic ghrelin, which is released by the stomach before food intake, as well as potential gut-brain communication through SCFA, i.e. acetate, propionate and butyrate. In mice it has been shown that acetate administration had an appetite-suppressing effect by surpassing the blood-brain-barrier and directly signalling to hypothalamic neurons (Frost et al. 2014). It remains unclear in which direction and through which mechanism SCFA might influence appetite. Evidence suggests both peripheral and central effects of SCFA on appetite, namely, appetite-inducing and -suppressing effects likewise acting on ghrelin, GLP-1 and PYY, as well as effects on reduced hedonic response to food cues after ingestion of prebiotic-propionate compounds (Han et al. 2021). All studies investigating prebiotics in the latter review, namely two human and three murine studies, showed a satiety-inducing effect of prebiotic supplementation compared to equicaloric placebo interventions after 1 to 16 weeks. Although related to modulating satiety, it remains unclear in which timeframe fiber intake affects satiety and which types of fiber act as appetite regulators in humans (M. J. Clark and Slavin 2013).

Overall, postprandial metabolic response affects brain activity via gut-brain signalling, showing distinct modulatory effects of appetite-stimulating (ghrelin) vs. appetite-suppressing (GLP-1, PYY and others) hormones on prefrontal cortex and insula compared to subcortical cortex including hypothalamus and amygdala (systematic review including 40 studies (Zanchi et al. 2017)) and yet to be determined mechanisms for SCFA signalling.

Besides effects on metabolic health and appetite regulation, habitual dietary patterns influence gut microbial composition and gut metabolic activity (Fan and Pedersen 2021). In turn, gut microbes are determinants of host energy-harvesting efficacy by modulating host energy uptake and homeostasis (Cani et al. 2019). It is established that obesity relates to imbalances in gut microbial profiles, which may be linked to the role of gut microbiota in the pathogenesis of the condition (Muscogiuri et al. 2019; Tilg and Moschen 2014). In contrast, gut composition in obese individuals has been shown to benefit from certain medication use, such as statins commonly used as cholesterol-lowering drugs (Vieira-Silva et al. 2020). Also, bariatric surgery leads to significant shifts and improvements in gut microbiome and metabolome, besides drastic weight loss success (Aron-Wisnewsky, Doré, and Clement 2012; Ilhan et al. 2020).

While gut microbial interactions with host metabolism have been shown extensively, links to behaviour and brain health remain unclear (Dalile et al. 2019; Rogers et al. 2016). Fiber and polyunsaturated fats have been proposed to be neuroprotective in the long-term by preserving structural integrity of the brain through anti-inflammatory properties (Muth and Park 2021), yet primary data on brain structure is missing. Links to neurobiological health and disease in humans remain scarce, and most evidence stems from research on autism spectrum disorder, neurodegenerative diseases (such as Parkinson's disease) and mood disorders (Morais, Schreiber, and Mazmanian 2021). Indeed, prebiotics, probiotics and SCFA

administration may elicit anxiety- or stress-releasing effects mediated by the gut microbiome (Dalile et al. 2020), with higher efficacy in clinical populations, including depression and anxiety disorders (Liu, Walsh, and Sheehan 2019). Yet again, primary data on brain function is missing.

In sum, although causal evidence in humans is limited, dietary fiber intake-related gut microbiota signalling might be a putative modulator of human health and behaviour acting via endocrine, immune or neuronal pathways.

1.6 Mechanisms III: Mood and personality

Next to physiological mechanisms, psychological factors related to high fiber diets will be outlined here.

Psychological factors related to food intake play an important role in food decision-making and health status. Obesity and depression have been shown to be reciprocally linked, displaying a detrimental vicious cycle for health (Luppino et al. 2010). In the case of plant-based dieters restrictive eating has been associated with higher risk for depressive symptoms and lower anxiety scores, which were different for dietary subgroups and dependent on the continent of interest (meta-analysis of 13 studies with n = 49,889 participants (Ocklenburg and Borawski 2021)). Restrictive dieting may be linked to depressive symptoms for various reasons, such as social exclusion, isolation or stigma. Indeed, plant-based diets have been associated with the expression of a personal and social identity (Nezlek and Forestell 2020), possibly leading to higher emotional instability and social dissatisfaction if being part of a social minority.

Contrastingly, healthy dietary intake, including high fiber, was related to lower depressive symptoms and anxiety in observational (meta-analysis: (Lassale et al. 2019)) and interventional studies (review: (Taylor and Holscher 2020)). Protective effects of plant-based diets on depression may stem from anti-inflammatory properties and microbiota-induced modification of depression-related gene expression modulating neurotransmitter release, such as higher tryptophan and serotonin production (Swann et al. 2020).

Besides links to mood, differences in personality traits for regular plant-based dieters have been observed, namely higher extraversion (Forestell and Nezlek 2018) and more openness (Pfeiler and Egloff 2018) in vegetarians.

Overall, food-mood relationships are prone to reverse causation due to underlying multidirectionality of those, confounding of lifestyle factors (Firth et al. 2020) and limitations in dietary assessment methodology (Ioannidis 2018). It remains unclear whether mood is affected by single meals different in fiber content and whether personality differences are associated with or caused by long-term shifts in diet and whether those replicate persistently across various demographic groups.

2 Objectives

My dissertation aims to investigate whether diet has an influence on eating choices and to elucidate the complex interplay between food intake and host behaviour, with a focus on obesity. Specifically, I looked at plant-based diets or RYGB as a modulator of this interplay, with a specific focus on gut-brain communication by SCFA signalling as a mechanistic pathway of interest. Further, I examined weight-mood-personality associations of long-term dietary patterns (**Figure 2**).

My thesis integrates findings of three publications with the overarching topic of (un)healthy eating behaviour and diet mechanistically linking to reward-related brain functional connectivity, gut markers and personality. **Publication 1** (Heinrichs et al. 2021) investigates longitudinal differences in brain circuits post-RYGB compared to waiting list control group, that may be one neural mechanism explanatory of weight loss success in obesity. **Publication 2** (Medawar, Haange, et al. 2021) explores links between gut microbiota abundance, eating behaviour traits and dietary intake, including SCFA metabolism in the host, in two independent cross-sectional samples. This study includes both overweight, and post-RYGB groups with age-, sex- and BMI-matched control groups. **Publication 3** (Medawar et al. 2020) examines associations of lower animal-based food intake on weight status, depressive symptoms and personality traits in a cross-sectional large cohort of 8,943 adults.
Further, I conducted a within-subject cross-over human dietary intervention study (**GUT-BRAIN study**, ClinicalTrials.gov NCT03829189, preregistered as Medawar, Thieleking, and Witte 2019) to test the effect of a two-week high fiber intervention on gut-brain communication and reward sensitivity for food. Also, in a series of three large-scale online studies (n_{meals} = 16,379) I investigated the effects of a single meal on satiation and mood contrasting plant-based to animal-based meals (**Mensa study,** preprint: Medawar, Zedler, et al. 2021).

Additionally, I set my PhD off with a systematic review synthesizing evidence of 27 randomized controlled trials, plus five additional studies, investigating the effects of plant-based diets on the body with a particular focus on the brain (Medawar et al. 2019) and recently published a meta-analysis on the effects of dietary polyphenols on cognition (de Vries, Medawar et al. 2021). Also, I contributed to two first author publications with a methodological focus that covered between-scanner reliability of structural measures in longitudinal brain imaging studies (Medawar, Thieleking, et al. 2021), and the creation of an open database for experimental art stimuli to be used in (fMRI) settings (Thieleking, Medawar et al. 2020). Further, I extended an existing food stimuli database by dietary fiber ratings (Medawar, Thieleking, and Witte 2021a) and developed a nutrient scoring pipeline for a commonly used food frequency questionnaire (FFQ) to estimate daily fiber intake (Medawar, Thieleking, and Witte 2021b) to enable addressing research questions on fiber intake.

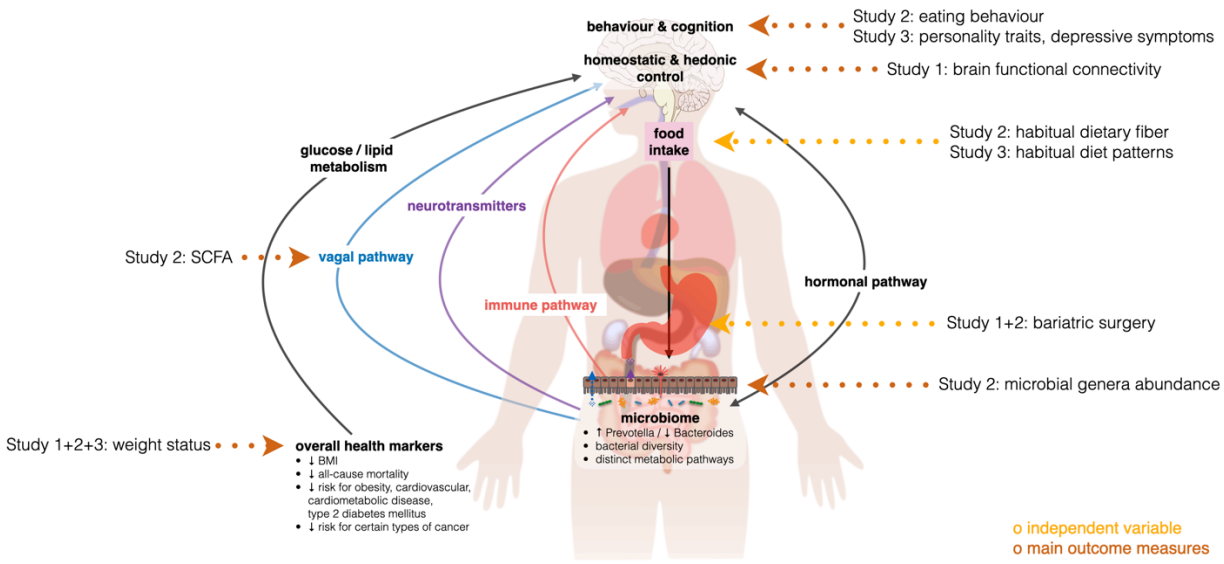

Figure 2: Overview of the objectives of this dissertation. Figure adapted from Medawar et al. (2019).

3 Methods

Detailed methodologies, including study design, participant inclusion/exclusion criteria, MRI preprocessing (if applicable), and statistical analysis are described in the methods section of the respective publications.

Study Design & Participant information

In **Study 1**, participants were included in the **ADIPOSITAS study** carried out at the Charité University Medicine Berlin, and either underwent bariatric surgery (n = 33, 26F) or were waiting list controls (n = 15, 11F), waiting for their health insurance's approval to undergo surgery. All participants were screened before surgery/control and 6 and 12 months after. The final sample entailed 48 morbidly obese individuals (37F; aged 44.2 ± 11.9 SD years, range 21–68). 60% of participants had clinically diagnosed hypertension, 4% had type 2 or type 1 diabetes, and 6% reported to smoke. The final dataset comprised 101 MRI datapoints.

In **Study 2**, data from two independent studies carried out at the Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, was combined: i) cross-sectional data from the so-called **GUT-BRAIN Study** including young, overweight adults (n = 27 (9F), 21-36 years, BMI 25-31kg/m^2), drawn from a randomized clinical trial (Clinical Trials registration NCT03829189), following a typical Western omnivorous diet and deeply screened for habitual dietary patterns, alcohol and caffeine intake, smoking and physical activity, and ii) cross-sectional data from the **BariRes Study** (in cooperation with the University Clinic of Leipzig, Leipzig) in patients two years after bariatric surgery with either good or bad response, and age-, gender- and BMI-matched controls ("good responders": n = 11 (7F), 41–70 years, BMI 25–29 kg/m^2; "bad responders": n = 12 (9F), 31–67 years, BMI 41–62 kg/m^2; overweight: n = 8 (5F), 41–58 years, BMI 25–29 kg/m^2; obese: n = 9 (6F), 26–70 years, BMI 41–48 kg/m^2).

In **Study 3**, data was taken from the baseline assessment of the population-based "Leipzig Research Centre for Civilization Diseases" (**LIFE-ADULT cohort study**) (Loeffler et al. 2015), which aims to investigate predictors and developments of common NCDs, such as cardiovascular diseases, obesity and depression. This analysis included n = 8,943 (4,609F) middle-aged individuals (mean ± SD: 56.6 ± 12.5 years, 18–82 years) with a very wide BMI range (mean ± SD: 27.3 ± 4.9 kg/m^2, 16–57 kg/m^2). About 2% of the sample (n = 237) reported to have adopted an exclusively vegetarian diet at least once throughout their life, and about 5% (n = 547) a mainly vegetarian diet.

The institutional ethics boards of the Charité University Medicine Berlin and Medical Faculty of the University of Leipzig raised no concerns regarding the study protocols and all participants provided written informed consent (Study 1: EA1/074/11, Study 2: 228/18-ek and 027/17-ek, Study 3: 263/09-ff).

Data Acquisition

Anthropometry. In all **Studies 1+2+3**, BMI was assessed by measuring body weight (kg) and body height (m) with scales and tape measure by the study personnel. For longitudinal studies, weight loss was calculated as a difference between two assessments.

Bariatric surgery. In **Studies 1+2**, patients underwent weight loss surgery, either sleeve gastrectomy or gastric banding, which result in a reduction of stomach volume by removing parts of the stomach along the curvature or inserting an inflatable band around the stomach,

respectively, while preserving the small intestine and digestive flow, or RYGB, where a small pouch is formed from the proximal stomach and connected to the jejunum. In **Study 1**, all methods had been performed (RYGB: 15, VSG: 12, GB: 1, NA: 5), and in **Study 2** RYGB only.

Questionnaires. In **Study 2**, questionnaires related to eating behaviour were administered, i.e. Three-Factor Eating Questionnaire (TFEQ) (Löffler et al. 2015), Eating Disorder Examination Questionnaire (EDEQ) (Hilbert et al. 2007) and FFQs (including DEGS-1) (Haftenberger et al. 2010) to assess habitual dietary intake. In particular, we developed a nutrient scoring pipeline, to compute daily nutrient intake based on self-reported dietary habits ("FFQ Nutrient scoring": Medawar, Thieleking, and Witte 2021b). We did this by combining computed mean daily portion [g] based on DEGS-1 FFQ and corresponding nutrient information based on reference nutrient data (using the German Nutrient Reference Database "Bundeslebensmittelschlüssel" version 3.02) for each of the 53 items. This resulted in mean daily intake of macro- and micronutrients, e.g. daily fiber intake in grams. In **Study 3**, self-reported questionnaire data was used to assess personality traits (NEOFFI) (Costa and McCrae 1989) and depressive symptoms (Center for Epidemiological Studies-Depression, CES-D) (Radloff 1977). To assess food intake habits based on intake frequency over the last 12 months, a dietary restriction score regarding animal-based products was computed.

Structural and functional magnetic resonance imaging (MRI). In **Study 1**, head MRI was performed with a 12-channel head coil on a 3 Tesla Trio, Siemens (Erlangen, Germany) with the syngo B17 software. Anatomical MRI was acquired using a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) pulse sequence. rsfMRI was acquired with a TR of 2300 ms and TE of 30 ms for 5:45 min. Preprocessing was done with three different pipelines (minimal, using ICA-AROMA and CompCor, using ICA-AROMA and CompCor and global signal regression).

Gut microbiota assessment. In **Study 2**, stool samples were collected using home kits to assess gut microbiome diversity, genera abundance and metabolic activity using metabolomics in one sample. 16S rRNA DNA sequencing was used for microbial community analysis, based on V3-V4 variable regions of the 1 S rRNA genes, that were amplified by PCR and a library was constructed, followed by paired-end 2x250bp Illumina sequencing (performed by GENEWIZ Germany GmbH, Leipzig). Taxonomical mapping and relative abundance calculations were done based on amplicon sequence variants (ASVs) by collaborations partner at the Helmholtz Centre for Environmental Research (UFZ), Leipzig. SCFA in stool and serum were measured using liquid chromatography-mass spectrometry (LC-MS).

Data Analysis

Functional connectivity. In **Study 1**, we used seed-to-voxel connectivity analysis with two regions of interest as seed, i.e. NAc for the reward network and the precuneus for the DMN. After creating individual masks based on FreeSurfer segmentation, standardized timeseries from seed regions and whole brain were extracted. Statistical analysis was performed with linear mixed models in the Sandwich Estimator Toolbox embedded in SPM12 to account for unequal sample size and missing datapoints. The original preregistration and its further developed extension, as well as open code and unthresholded brain 3D maps are publicly available (see original publication).

Correlational analysis. For **Study 2**, analyses were exploratory and intended to generate hypotheses for the interventional **GUT-BRAIN Study**, taking appropriate considerations for explorative analyses into account (Simmons, Nelson, and Simonsohn 2011). Relative abundance of bacterial genera that appeared in at least 80% of biosamples, defined inclusion of datapoints to the overall correlational matrix with all variables of interest (37 variables in total, see above). Statistical significance was set to $p_{FDR} < 0.05$. For those genera that were significantly associated with eating behaviour (TFEQ traits and/or hunger ratings, $p_{FDR} < 0.05$) correlations with weight status and RYGB treatment success in sample 2 were tested. Non-parametric Kruskal–Wallis tests were performed to test group differences across overweight, obese, good and bad RYGB responders.

Linear regression models. For **Study 3**, I computed linear regression models for each predictor of interest, and extended those with confounding variables of no interest in a step-wise process. For personality traits, I ran a multivariate analysis of covariance to include all five traits into one model. Variables were checked for normal distribution or otherwise transformed, and I corrected all analyses for multiple comparisons using the Bonferroni method. All analyses were preregistered and code is openly shared: https://osf.io/m7hxk/.

4 Results

In **Study 1**, confirmatory analyses did not show any significant effects of bariatric surgery on functional connectivity of the reward network or the DMN, neither for whole-brain or within-network analysis. Exploratory analyses revealed that BMI decrease after surgery compared to baseline ("treatment success") resulted in significantly increased connectivity of the reward network with medial posterior frontal regions (**Figure 3a**). Significant clusters were reliable in spatial location across different preprocessing pipelines.

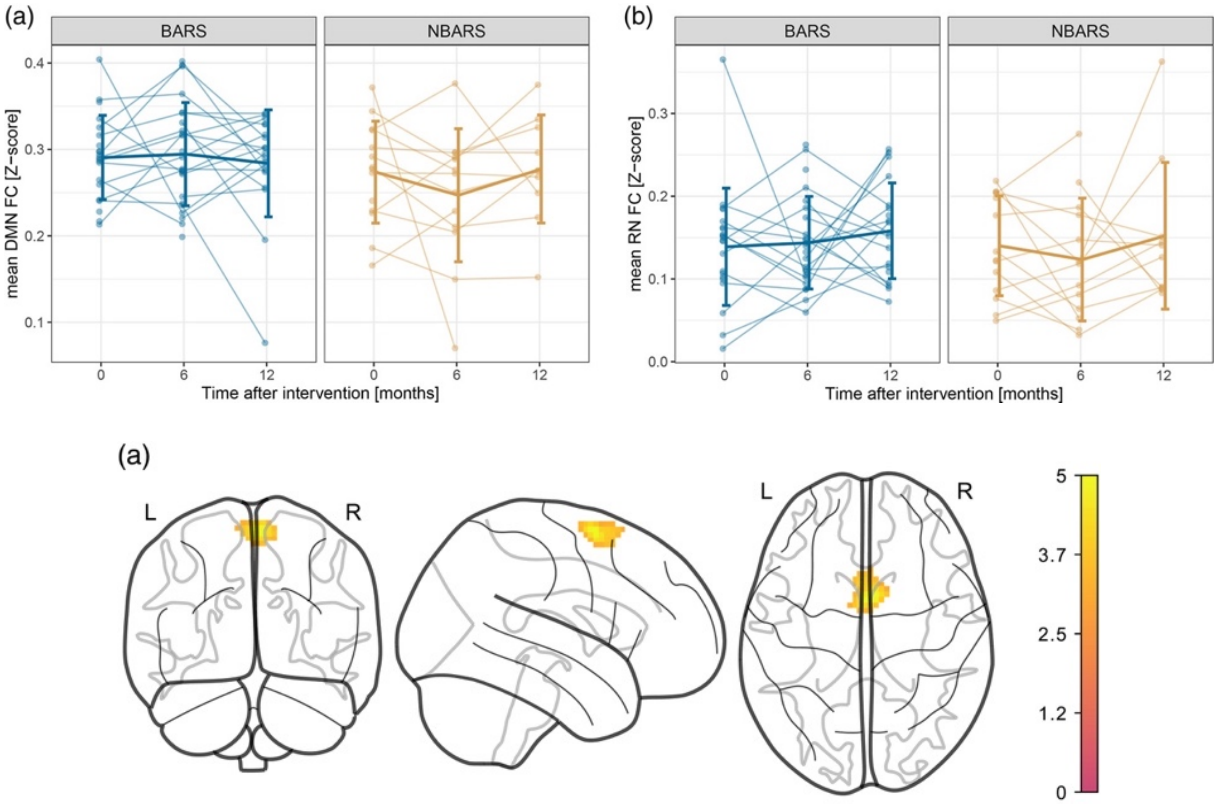

Figure 3a: Top panel: Mean network connectivity per group across timepoints by group for bariatric surgery group (BARS) and the waiting-list control group (NBARS); transparent lines show individual trajectories, opaque lines depict mean ± SD trajectories by group. Bottom panel: Stronger BMI decrease is associated with increased functional connectivity between NAc and posterior-medial frontal region, adjusted for age, sex, average BMI, and logarithm of mean framewise displacement (log mFD), denoised with AROMA + CC. Legends denote empirical Z value. DMN: default mode network; RN: reward network; FC: functional connectivity.
Figures taken from Heinrichs et al. (2021).

In **Study 2**, correlation analysis in the young, overweight sample showed two groups of microbial genera differentially linked to host health status and eating behaviour. Seven genera correlated with healthier eating behaviour (Alistipes, Blautia, Clostridiales cluster XVIII, Gemmiger, Roseburia, Ruminococcus, Streptococcus), while five genera correlated with unhealthier eating (Clostridiales cluster IV and XIVb, Collinsella, Fusicatenibacter, Parabacteroides) (**Figure 3b**). Three genera were linked to habitual dietary fiber intake (+: Clostridium XVIII; -: Collinsella, Parabacteroides). Links between fiber intake or genera and SCFA remained elusive. Relative abundance of all genera linked to unhealthy eating and abundance of Parabacteroides alone, were significantly informative of treatment success post-bariatric surgery. Higher abundance of Parabacteroides related to lower weight loss and higher overall unhealthy eating traits in the two bariatric patient groups (**Figure 3b**).

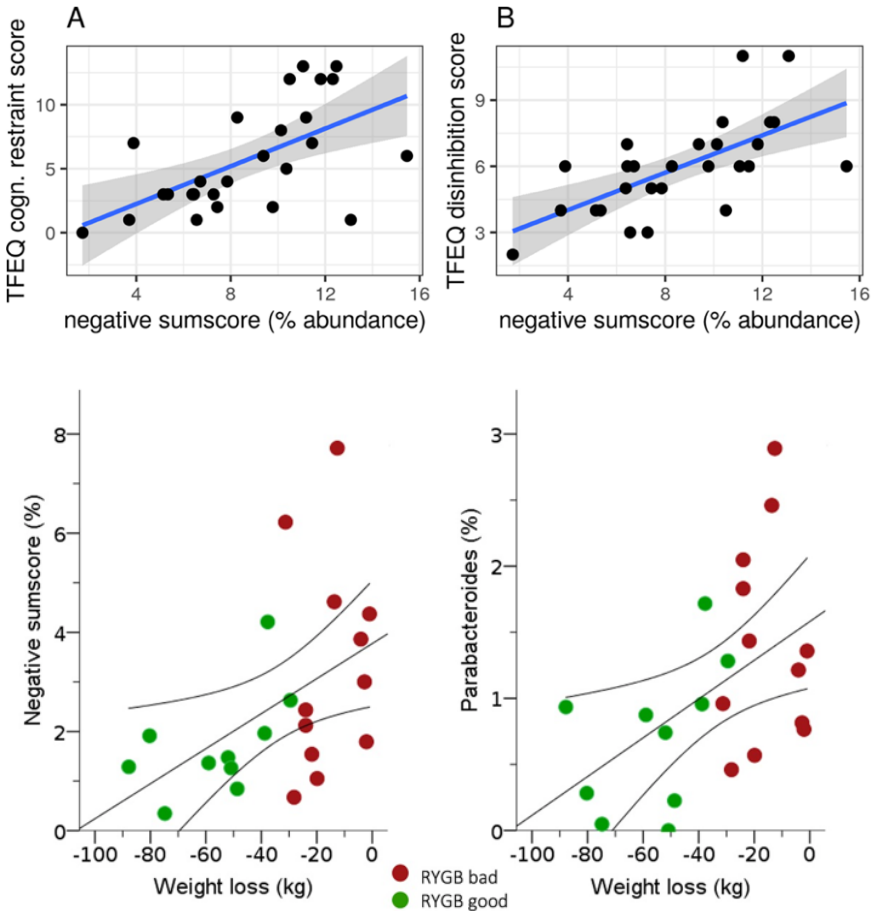

Figure 3b: Microbiota genera abundance relates to unhealthy eating behaviour traits. RYGB: Roux-en-Y gastric bypass; TFEQ: Three-Factor Eating Questionnaire. Figures taken from Medawar, Haange, et al. (2021).

In **Study 3**, linear regression models firstly showed that lower habitual intake of animal-based products was significantly linked to lower BMI in a sample representative for the general population in Leipzig (**Figure 3c**). Secondly, there was no significant association between diet and depressive symptom scores. Thirdly, personality, i.e. lower extraversion, was significantly related to lower intake of animal-based food items.
Indeed, a multitude of personality traits was associated with higher depressive symptom scores, i.e. higher neuroticism, lower extraversion, lower agreeableness and lower conscientiousness. Also higher depression scores significantly related to higher BMI. Overall restriction of food items was also significantly linked to lower BMI, but also to higher depression scores. Moreover, overall dietary restriction showed significant links to lower agreeableness and higher conscientiousness.

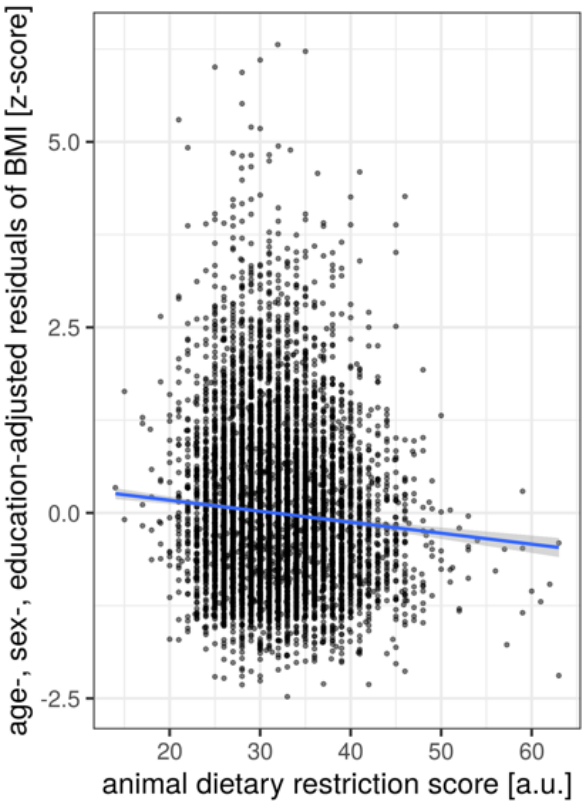

Figure 3c: Association between body-mass-index (BMI) and demographic and animal dietary restriction score; residuals plotted according to regression model 1 (sample 1 n = 8943). Line gives regression fit. Point size = 1. Abbreviations: a.u.: arbitrary units. Figure taken from Medawar et al. (2020).

5 Discussion

5.1 General considerations

The herein presented studies provide evidence of distinct psychophysiological mechanisms related to eating behaviour based on a series of diverse methodological approaches. On the one hand, therapeutical interventions in clinical populations have the benefit of controlled settings, close monitoring and, in case of bariatric surgery, drastic intervention effects. Yet, the respective evidence is restricted in its applicability to specific samples only, therefore not easily transferable to the general population. On the other hand, evidence from studies in the general population on diet-related topics are more generalisable. Yet, dietary intake is challenging to assess accurately or to modulate by interventions in free-living populations due to confounding factors. Therefore, an overall strength of my dissertation is the combination of different methods and populations, spanning from clinical samples (**Studies 1+2**), deeply phenotyped samples representative of the general population (**Study 2**) and large samples of the general population (**Study 3**). I will discuss general considerations first to facilitate interpreting study results and evaluating study quality, followed by results, strengths and limitations of each study in detail in the next paragraphs.

5.2 Study I: Power and control groups in fMRI studies

When assessing study quality of fMRI studies on the effects of bariatric surgery, several factors in the study design should be considered: sample size (Szucs and Ioannidis 2020; Button et al. 2013), multiple datapoints in time of one individual to account for within-subject variability (Thiese 2014) and adequate control groups determine study quality. Indeed, most studies examining RYGB-induced changes in functional connectivity either have no or a normal-weight control group. Confounding metabolic differences due to morbid obesity compared to normal-weight should be expected and therefore, waiting list control patients may be the control group that most closely matches the intervention group. Additionally, clinical interventions integrating brain MRI remain effortful for clinical staff and patients, as time in the clinical setting is tightly scheduled, MR scanners are not always available or of suitable width for pre-surgery patients, and especially in longitudinal designs compliance for follow-up visits is hard to control. Additionally, reporting practises in themselves can increase the level of evidence, such as preregistering hypotheses and the statistical analysis plan, reporting effect sizes and applying Bayesian statistics, all of which improve credibility and interpretability of the results (Nosek et al. 2018).

In **Study 1**, we included waiting list patients as controls, sample size overall was rather small (n = 48), yet larger than many other studies, the fMRI analysis was extensively preregistered, and unthresholded maps were made public. We implemented three different preprocessing pipelines, and found no substantial differences in the results, which suggests that the analysis method is rather secondary in our case, but reliable across methods. Primary analysis was reported as null results, adding important evidence to the overall literature. Exploratory analysis showed that treatment success related to increased connectivity between the reward network and a cluster which maps to the superior frontal gyrus and supplementary motor area, attributed to the salience network and likely involved in action planning. Interpretation of this finding remains speculative, but may point towards better signal processing between reward action initiation processes, signifying improved reward to action translation in obesity, potentially linked to less impulsive decision-making. Further, head motion during scanning related to increased connectivity between the reward network and a cluster in the motor cortex. This finding is important to be considered in future studies with a similar focus

adjusting for in-scanner head motion, but also exemplifies how additional confounding factors should be measured and investigated.

Next to recruiting adequately powered samples of patients for each condition, data pooling and meta-analyses are promising future directions. Further, besides resting-state functional connectivity as an outcome measure of interest, more targeted brain outcome measures might be of relevance for RYGB-induced effects, such as food cue reactivity (Hermann et al. 2019) or food craving, that can be linked to psychological and behavioural outcomes that may be provided by the participants during brain imaging.

5.3 Study II: Gut-brain axis lacks intervention studies in humans

Most hypotheses on gut-brain communication and its mechanisms stem from animal studies, some mostly observational human studies and many literature reviews speculating on pathways of interest.

The associative nature of gut microbiome studies in humans provides valuable insights into possible mechanisms and pathways of interest, yet causality remains to be proven by intervention studies. In particular, cross-sectional analyses of the gut microbiome are prone to overseeing individual baseline differences in gut composition, temporal shifts and dynamics and require either tight controlling for or assessing of confounding factors, such as lifestyle, mode of birth, mode of feeding, antibiotic treatment, alcohol intake and many others or close matching when comparing groups of individuals (Vujkovic-Cvijin et al. 2020).

In our analysis in **Study 2**, all data was of a cross-sectional nature *sensu strictu*, yet both samples were closely matched to result in homogeneous groups with similar dietary patterns and weight status in sample 1, and in post-surgery groups with closely matched control groups comparable to post-surgery weight status in sample 2. Since post-surgery groups have been defined on the basis of treatment success, group comparisons reflect a longitudinal element related to therapy outcome. Also, we assessed various potential confounders (sex, coffee intake, time of day, seasonality) and tested their influence on alpha diversity, resulting in no significant associations. Confounders in the RYGB groups were harder to assess, as less detailed information was collected during the study and certain factors were by nature different from surgery to control groups, such as medication use for alleviating gastrointestinal symptoms, e.g. protein pumps inhibitors. Relations between eating behaviour and SCFA remained elusive.

Yet, there are certain limitations to the study. Firstly, fiber intake was based on self-reported dietary data, that are subject to reporting bias. Secondly, it remains unclear if relative genera abundance can be compared from one sample to another with different weight status and differences in biosample processing, even though DNA extraction, DNA sequencing and bioinformatical analysis were performed similarly. Thirdly, due to the cross-sectional nature of the analysis, it remains unclear, if eating habits prompted microbial genera shifts or if genera induced certain eating behaviour.

Indeed, human intervention studies investigating gut-brain communication related to dietary fiber remain scarce, and mostly assess intervention effects of prebiotics on one particular outcome, e.g. stool frequency (Micka et al. 2017), SCFA levels (Baxter et al. 2019) or stress levels (Dalile et al. 2020), but not in combination or with a focus on food decisions. Improving knowledge on causality of gut-brain pathways requires interdisciplinary approaches, that integrate multiple outcomes and biomarkers into one study, to enable tracking intervention

effects within the same setting. Ideally, such interventions should modulate one factor only (such by administering a dietary supplement) in a free-living population and strictly controlling for or assessing potential confounders. Moreover, the intervention condition should have a control condition in the same individual (cross-over within subject design) to eliminate inter-individual differences in the gut microbiome.

Lastly, methodology of assessing the gut microbiome and markers of interest need to be discussed. The most common method for microbial diversity analysis is 16S rRNA DNA sequencing, and since more recently shotgun genome sequencing, which has higher detection power for less abundant genera (Durazzi et al. 2021). Therefore, methodology and particularities in the analysis could affect outcomes and therefore comparability of results across different studies.
Also, beyond metagenomics, proteomics, metabolomics and functional pathway analysis (Zhang et al. 2019) provide more functional insights into bacterial composition and their role for host metabolism and should be considered alongside with microbial composition, potentially constituting even more relevant markers. Importantly, multi-omics analysis requires precautions in data sampling, such as seamless freezing of biosamples or the use of specific buffers if collected at room temperature.

5.4 Study III: Evaluation of the assessment of dietary intake based on self-report

Studies investigating nutrition cross-sectionally or epidemiologically are dependent on assessing food intake using self-reported dietary diaries, dietary recall administered by nutrition experts or other observational measures. Although, self-reported measures in free-living populations may be criticized for low accuracy and reporting bias leading to under- or overreporting (Ioannidis 2018), there are advantages of FFQs based on self-report (Subar et al. 2015). Those are low costs, easy implementation, low time investment and the possibility of self-administration. The field of nutrition sciences aims to improve dietary assessment methodology by digitalizing reporting methods to enable low-threshold integration into everyday life of study participants, for example by smartphone-based tools (König et al. 2021). Moreover, to avoid self-reporting and recall bias, the development of algorithm-based food intake measurement tools in real-world environment (Oliveira Chaves et al. 2021), in particular using photos of meals (Ruede et al. 2021), could spur further innovation and improve accuracy of food intake assessment.

In **Study 3**, indeed quality of food intake data was limited, due to lack of information on the quantity of food intake and a limited spectrum of food items listed in the questionnaire. Yet, the questionnaire asked for food intake over the last 12 months and included details on low-fat products. My analysis was based on a restriction score looking at excluded food items over a timeframe of 12 months and is therefore presumably a strong and reliable indicator of actual food intake and exclusion of certain food groups. To ensure replicability and transparency, precise scoring considerations and scoring code were made public. Overall, I was able to replicate links between restricted animal-based food intake and lower weight status, which supports the notion that the herein used food scoring adequately reflects habitual dietary patterns.

In **Study 2**, I implemented a well-validated FFQ based on frequency and quantity that also includes plant-based items, types of oil and whole-grain products (for further details see the *publication* of **Study 2**). Beyond scoring of food intake in grams per item as provided by the

questionnaire's manual, I developed an open code nutrient scoring pipeline to get detailed information on daily intake of macro- and micronutrients based on the self-reported food intake data. This enabled detailed assessment of individual fiber intake as well as correlational analysis with other markers of interest in **Study 2**.

Overall, dietary assessment in epidemiological studies remains challenging and an approximation to actual food intake, yet methods are well established and validated in most cases (Subar et al. 2015). For more detailed analyses on specific nutrients, more objective markers are needed, e.g. serum- or urine-based biomarkers (Playdon et al. 2016), and self-reporting may be improved with the help of digital tools. Longitudinal studies tracking individuals in time and dietary intervention studies have the benefit of reduced reporting bias due to higher within-subject comparability and targeted interventional modulation increasing level of evidence and reliability of results.

5.5 Ongoing projects: Intervention studies and meta-analyses

To improve the mechanistic understanding of diet-brain relationships, as well as in order to improve conservative treatment options for obesity, interventional studies with multiple timepoints will help to elucidate causality of putative links. High evidence stems from randomized controlled trials (RCTs) and meta-analyses synthesizing evidence from single studies. We therefore, designed two interventional studies: firstly, a within-subject cross-over human dietary intervention (**GUT-BRAIN study**, Medawar, Thieleking, and Witte 2019) investigating the effect of a two week high fiber diet compared to equicaloric placebo on food wanting and its neural correlates, and changes in gut composition and SCFA metabolism. Secondly, to examine psychophysiological effects of a single meal, we conducted three large scale smartphone-embedded studies based in German university cafeterias comparing plant-based to animal-based meals (**Mensa study**, Medawar, Zedler, et al. 2021). Further, a systematic review on the influence of lifestyle factors on gut microbiome composition is currently performed (Akan, Medawar, and Witte, *in prep*).

6 Conclusion

Overall, advancing knowledge on effective treatments for and mechanisms related to obesity is crucial to addressing the two-fold problem of malnutrition and the climate crisis. Due to their co-occurrence and shared underlying societal drivers, the term *"The Global Syndemic"* of obesity, undernutrition and climate change has been coined (Swinburn et al. 2019). Next to posing a burden on human health, obesity causes an additional climate burden, that has been estimated to about 700 megatons per year of CO_2 equivalents (CO_2eq) or 1.6% of total global GHG (Magkos et al. 2020), stemming from metabolic activity, excess food intake, and higher mobility demands due to greater body weight. Therefore, reducing obesity prevalence and improving overall dietary quality leads to co-beneficial effects on human and planetary health (M. A. Clark et al. 2019). Indeed, even though the adoption of current national dietary guidelines would lead to a decrease in premature mortality rate of 15% and a reduction of GHG by 13% caused by the food system in a modelling study across 85 countries, most guidelines still do not meet global health and environmental targets (Springmann et al. 2020). In sum, next to the need of political goals to counteract The Global Syndemic to become even more ambitious, a more comprehensive and in-depth understanding of mechanisms modulating and maintaining diet-brain-behaviour is needed to adopt more human- and planetary-health diets.

Precisely, research questions and methods need to be further refined to increase the efficacy of obesity prevention and treatment options. Expanding research on invasive surgical treatment remains a challenge due to financial and time constraints in study design due to the primary clinical justification to treat patients. Therefore, basic research should expand on conservative treatment options, also with the prospect to advance preventative strategies to avoid steadily increasing prevalence of overweight and obesity. Studies will benefit from investigating the whole BMI spectrum to detect sensitive weight groups, investigating specific single dietary components, such as dietary fiber, refining tasks to characterize dimensions of reward processing for food decision-making and examining candidate mechanistic routes of the gut-brain-axis in animals and humans in detail.

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Statutory Declaration

I, Evelyn Medawar, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic „Psychophysiological investigations on eating behaviour / Psychophysiologische Untersuchungen zum Essverhalten“ 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; 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.

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Date

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Signature of the doctoral candidate

Declaration of the contribution to the publications

Evelyn Medawar contributed as follows to these publications:

Publication 1: Heinrichs, H. S., Beyer, F., **Medawar, E**., Prehn, K., Ordemann, J., Flöel, A., & Witte, A. V. (2021). Effects of bariatric surgery on functional connectivity of the reward and default mode network: A pre-registered analysis. *Human Brain Mapping*, 1– 17.

- Impact Factor (2019) = 4.421 (#3 out of 14 in Neuroimaging)
- Contribution in detail: Evelyn Medawar contributed to the study design of the already existing dataset and took major part in the preregistration of the analysis of the rsfMRI data. She also participated in writing and reviewing the manuscript.

Publication 2: **Medawar, E.**, Haange, SB., Rolle-Kampczyk, U., Engelmann, B., Dietrich, A., Thieleking, R., Wiegank, C., Fries, C., Horstmann, A., Villringer, A., von Bergen, M., Fenske, W. & Witte, A.V. (2021). Gut microbiota link dietary fiber intake and short-chain fatty acid metabolism with eating behavior. *Translational Psychiatry* 11, 500.

- Impact Factor (2019) = 5.280 (#23 out of 216 in Psychiatry)
- Contribution in detail: Evelyn Medawar designed the study and the here presented analysis of the dataset. She is mainly responsible for data collection, data curation and data analysis of sample 1 (cross-sectional study) including blood, stool and MRI data. She further helped to harmonize both datasets. She further ran all analyses and visualized all figures and tables (Figures 1-6, Tables 1-3). She also coordinated the publication process. She provided open data alongside with the manuscript for publication.

Publication 3: **Medawar, E.**, Enzenbach, C., Roehr, S., Villringer, A., Riedel-Heller, S., & Witte, A. V. (2020). Less Animal-Based Food, Better Weight Status: Associations of the Restriction of Animal-Based Product Intake with Body-Mass-Index, Depressive Symptoms and Personality in the General Population. *Nutrients*, 12(5), 1492.

- Impact Factor (2018) = 4.171 (#16 out of 86 in Nutrition and Dietetics)
- Contribution in detail: Evelyn Medawar contributed to the study design of the already existing dataset and was the main contributor of the preregistration. She conceptualized and computed the dietary scoring for this analysis on her own and scored the personality traits according to the manual. She further ran all the analyses and visualized all figures and tables (Figures 1-7, Tables 1-9). She coordinated the publication process. She also made code openly available on OSF.

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Signature of the doctoral candidate

Print versions of the selected publications

Publication 1

Heinrichs, H. S., Beyer, F., **Medawar, E.**, Prehn, K., Ordemann, J., Flöel, A., & Witte, A. V. (2021). Effects of bariatric surgery on functional connectivity of the reward and default mode network: A pre-registered analysis. *Human Brain Mapping*, 1– 17. https://doi.org/10.1002/hbm.25624

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI
Selected Categories: **"NEUROIMAGING"** Selected Category Scheme: WoS
Gesamtanzahl: 14 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NEUROIMAGE	102,632	5.902	0.125360
2	Journal of NeuroInterventional Surgery	5,583	4.460	0.015900
3	HUMAN BRAIN MAPPING	23,094	4.421	0.042760
4	NeuroImage-Clinical	7,868	4.350	0.027050
5	Brain Imaging and Behavior	2,979	3.391	0.008440
6	AMERICAN JOURNAL OF NEURORADIOLOGY	23,135	3.381	0.027120
7	NEUROIMAGING CLINICS OF NORTH AMERICA	1,191	2.632	0.001640
8	JOURNAL OF NEURORADIOLOGY	1,103	2.423	0.001810
9	JOURNAL OF NEUROIMAGING	2,219	2.321	0.004170
10	NEURORADIOLOGY	5,713	2.238	0.006020
11	PSYCHIATRY RESEARCH-NEUROIMAGING	5,414	2.063	0.007190
12	CLINICAL EEG AND NEUROSCIENCE	1,075	1.765	0.001690
13	STEREOTACTIC AND FUNCTIONAL NEUROSURGERY	1,724	1.635	0.002060
14	KLINISCHE NEUROPHYSIOLOGIE	54	0.111	0.000010

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RESEARCH ARTICLE

WILEY

Effects of bariatric surgery on functional connectivity of the reward and default mode network: A pre-registered analysis

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Abstract

Obesity imposes serious health risks and involves alterations in resting-state functional connectivity of brain networks involved in eating behavior. Bariatric surgery is an effective treatment, but its effects on functional connectivity are still under debate. In this pre-registered study, we aimed to determine the effects of bariatric surgery on major resting-state brain networks (reward and default mode network) in a longitudinal controlled design. Thirty-three bariatric surgery patients and 15 obese waiting-list control patients underwent magnetic resonance imaging at baseline, after 6 and 12 months. We conducted a pre-registered whole-brain time-by-group interaction analysis, and a time-by-group interaction analysis on within-network connectivity. In exploratory analyses, we investigated the effects of weight loss and head motion. Bariatric surgery compared to waiting did not significantly affect functional connectivity of the reward network and the default mode network (FWE-corrected $p > .05$), neither whole-brain nor within-network. In exploratory analyses, surgery-related BMI decrease (FWE-corrected $p = .041$) and higher average head motion (FWE-corrected $p = .021$) resulted in significantly stronger connectivity of the reward network with medial posterior frontal regions. This pre-registered well-controlled study did not support a strong effect of bariatric surgery, compared to waiting, on major resting-state brain networks after 6 months. Exploratory analyses indicated that head motion might have confounded the effects. Data pooling and more rigorous control of within-scanner head motion during data acquisition are needed to substantiate effects of bariatric surgery on brain organization.

KEYWORDS
bariatric surgery, default mode network, head motion, humans, longitudinal, magnetic resonance imaging, obesity, reward, waiting list, weight loss

Hannah S. Heinrichs and Frauke Beyer contributed equally to this study.

1 | INTRODUCTION

Obesity is a worldwide health issue, entailing huge personal and societal costs. Excess amount of body fat not only affects cardiovascular and metabolic health, but also increases the risk for cognitive decline and dementia later in life (Albanese et al., 2017). Conservative treatment options including behavioral therapy often do not yield the desired weight loss, especially in patients with very high BMI (>35 kg/m^2). Here, bariatric surgery, also known as weight loss surgery, is a viable option to rapidly induce weight loss and improve glycemic status. Common techniques like vertical sleeve gastrectomy (VSG) and gastric banding (GB) result in a reduction of stomach volume by removing parts of the stomach along the curvature or inserting an inflatable band around the stomach, respectively, while preserving the small intestine and digestive flow. Roux-en-Y gastric bypass (RYGB) is a more invasive surgical procedure, where a small pouch is formed from the proximal stomach and connected to the jejunum. Thereby, the ingested food bypasses a large portion of the stomach and proximal small bowel, resulting in complementary malabsorption of nutrients. Meanwhile, the disconnected biliopancreatic tract is re-anastomosed at a more distal part of the jejunum. Apart from reduced digestion efficiency and malabsorption of nutrients, altered food perception, appetite, and central regulation of food intake may also be responsible for surgery-induced weight loss (Brutman, Sirohi, & Davis, 2019; Mulla, Middelbeek, & Patti, 2017).

Precise mechanisms how bariatric surgery leads to altered appetitive signaling are yet to be elucidated. One option to address these questions on brain-behavior relationships is to use resting-state functional magnetic resonance imaging (rsfMRI), a technique capturing the dynamic organization of the brain. Functional connectivity networks, that is, brain regions with correlated neural activity over time, are in anatomical correspondence with specific brain networks involved in cognitive processes, including attention and executive control (Smith et al., 2009). The reward network, processing hedonic value and internal motivation, and the default mode network (DMN), a higher-order network, involved in interoception and governing shifts between external-internal processes, are promising candidates to mediate altered central regulation of food intake after bariatric surgery.

The reward network comprises the ventromedial prefrontal cortex (vmPFC), the nucleus accumbens (NAcc), the putamen, the amygdala, and the anterior insula (Liu, Hairston, Schrier, & Fan, 2011; O'Doherty, 2004). These brain regions have been suggested to guide food valuation processes and decision-making in humans (Bartra, McGuire, & Kable, 2013; Hare, Malmaud, & Rangel, 2011; Hutcherson, Plassmann, Gross, & Rangel, 2012; Schmidt et al., 2018). Frequently, obesity has been associated with hyperactivation of reward network regions during anticipation of (high-caloric) food cues, and in contrast, reduced activation to actual taste of these foods (Devoto et al., 2018; García-García et al., 2014; Meng, Huang, Ao, Wang, & Gao, 2020; Stoeckel et al., 2009), though this has recently been critically discussed (see Morys, García-García, & Dagher, 2020). RsfMRI studies also showed increased local functional connectivity of reward network regions, that is, NAcc, vmPFC, putamen, insula (Contreras-Rodríguez, Martín-Pérez, Vilar-López, & Verdejo-Garcia, 2017; Coveleskie et al., 2015; Hogenkamp et al., 2016), and altered connectivity with salience, homeostatic, and sensorimotor networks (Lips et al., 2014; Wijngaarden et al., 2015). In bariatric surgery patients, connectivity within the reward network (e.g., putamen and OFC) might be normalized by the surgery, however, the evidence is limited due to a lack of longitudinal obese control groups (Duan et al., 2020; Schmidt et al., 2021; Wiemerslage et al., 2016). Possibly, a reconfiguration of the fronto-striatal brain networks could emerge from altered gut signaling, for example, changes in ghrelin levels, via hypothalamic-striatal projections (Karra et al., 2013; Li et al., 2019) though hormonal mediators have been disputed by Zoon et al. (2018).

The DMN includes the posterior cingulate cortex (PCC)/precuneus, the medial prefrontal cortex (mPFC), and the inferior and lateral parietal cortex (Raichle, 2015) and is implicated in various functions, such as interpersonal cognition, episodic memory, prospective thought, and interoception (Buckner, Andrews-Hanna, & Schacter, 2008; Marsland et al., 2017). Higher cognitive function often depends on successful modulation of the DMN and communication across networks. Meanwhile, patterns of DMN dysfunction, on the other hand, have been demonstrated for various physiological and neuropsychiatric disorders (e.g., ADHD, type-2 diabetes, and mood disorders). Alterations in the DMN and its connectivity could consequently be a biomarker for pathophysiological mechanisms that predisposes individuals to the development or exacerbation of neuropsychiatric problems. Possibly, poor metabolic health common in obese individuals may act as a catalyst in that insulin resistance and altered cerebral glucose metabolism within the DMN augments a cascade that ultimately leads to the formation of pathology linked to cognitive impairments and even Alzheimer's disease (Buckner et al., 2008; Kenna et al., 2013). Higher BMI and obesity have been associated with a pattern of decreased functional connectivity within the DMN and increased functional connectivity of DMN regions to other networks, that is, salience and sensory networks in several resting-state and task-based rsfMRI studies (Beyer et al., 2017; Borowitz, Yokum, Duval, & Gearhardt, 2020; Chao et al., 2018; Ding et al., 2020; Doucet, Rasgon, McEwen, Micali, & Frangou, 2017; Kullmann et al., 2011; Sadler, Shearrer, & Burger, 2018; Wijngaarden et al., 2015). After bariatric surgery, a normalization of the connectivity between DMN and cognitive control and salience brain regions might occur, yet no study has included a longitudinal control group (Frank et al., 2013; Li et al., 2018; Olivo et al., 2017). In sum, while there is some evidence hinting to a role for DMN and reward network functional connectivity in altered regulation of food intake after bariatric surgery, the existing evidence is inconclusive. Most studies have investigated small cohorts of patients, without adequate obese control groups, and did not rigorously separate confirmatory from exploratory analyses (George et al., 2016).

Further, while higher BMI has been consistently associated with more head motion during rsfMRI (Beyer et al., 2017; Hodgson

et al., 2016), previous studies in bariatric surgery patients have not taken this important confounder of functional connectivity into account. In the present sample, we previously reported a group-by-time interaction on head motion (Beyer et al., 2020). Thus, we aimed to rigorously control for motion-related variance in our analyses. We had the following confirmatory hypotheses:

> **Hypothesis 1.** *Whole-brain functional connectivity of the reward network and DMN changes differently from baseline to follow-up in the bariatric surgery compared to a waiting-list control group.*

> **Hypothesis 2.** *Within-network functional connectivity of the reward network and DMN changes differently from baseline to follow-up in the bariatric surgery compared to a waiting-list control group.*

We tested Hypothesis 1 by investigating the interaction of bariatric surgery and time on reward network and DMN whole-brain functional connectivity. We pre-registered two denoising pipelines, and three covariate schemes. For Hypothesis 2, we performed a confirmatory analysis of the group-by-time interaction on aggregated, within-network functional connectivity, for two time points and the same covariate schemes. In exploratory analyses, we examined the whole-brain interaction effect for three time points, the effects of head motion on functional connectivity and whether weight loss, a proxy of treatment success, predicted changes in functional connectivity.

2 | METHODS

2.1 | Sample and study design

The ADIPOSITAS-study investigated the effects of bariatric surgery on brain structure and function in a prospective design at the Charité University Medicine Berlin, Germany. For more details, see Prehn et al. (2020). We used all data acquired until April 2019. The study design and primary outcomes (cognitive function and blood parameters) were registered at clinicaltrials.gov as NCT01554228. The study protocol was in accordance with the Helsinki Declaration and approved by the Ethics Committee of the Charité University Medicine Berlin (EA1/074/11). As neuroimaging was not covered in the clinicaltrials.gov registration, we pre-registered the present resting-state fMRI analyses on the Open Science Framework (OSF; https://osf.io/yp42s). We made additional changes (see https://osf.io/59bh7/) to the pre-registration after preprocessing the rsfMRI data, as we realized some aspects of the analysis were inadequately described in the initial pre-registration. For a comparison of the pre-registration and the manuscript, please visit https://osf.io/45n9f/. Participants were recruited from the Center for Bariatric and Metabolic Surgery at the Charité University Medicine Berlin. Inclusion criteria were, in accordance with German guidelines for bariatric surgery, a failure of conservative obesity treatment and either (a) a BMI > 40 km/m^2 or (b) a BMI > 35 kg/m^2 and at least one typical co-morbidity (e.g., type-2 diabetes, hypertension and nonalcoholic fatty liver disease; Mechanick et al., 2013). Participants were aged between 18 and 70 years and had no history of cancer, chronic inflammatory disease and addiction, other severe untreated diseases, brain pathologies identified in the MRI scan or cognitive impairments (defined as MMSE score < 24). In total, 51 participants out of the originally enrolled 69 subjects received MRI. Five data points of three subjects had to be excluded due to bad anatomical image quality (see below), which led to a final data set with 101 rsfMRI sessions. The final sample entailed 48 morbidly obese individuals (37 females; aged 44.2 ± 11.9 SD years, range 21–68). Participants of 60.4% had clinically diagnosed hypertension, 4.2% had type-2 or type-1 diabetes, and 6.2% reported to smoke.

Participants either underwent surgery ($n = 33$, 26 females) or were waiting list controls ($n = 15$, 11 females), who waited for their health insurance's approval to undergo surgery. Groupwise baseline characteristics are shown in Table 1. Measures were taken at baseline (BL), 6 (FU1) and 12 (FU2) months postsurgery/baseline appointment to capture both phases of rapid weight loss and maintenance (Maciejewski et al., 2016). Analyses were performed on all participants who provided at least one data point of rsfMRI data. Nineteen participants had complete data, 15 provided data for two time points, and 14 for one time point (for more details see Figure S1). The pre-registered analysis of changes from baseline to follow-up included 24 participants with both time points, in total 72 data points.

Fifteen patients underwent RYGB, 12 underwent VSG and 1 GB, for five patients in the intervention group, this information was not available. Participants arrived in the morning (between 07:00 and 12:00 a.m.) after an overnight fast. They underwent medical assessments including an interview, blood draw, and anthropometric measurements before having a 1 hr break for breakfast. MRI scanning was done after performing a psychological test battery (for details, see Prehn et al., 2020).

TABLE 1 Baseline characteristics of total sample

	BARS	NBARS
N	33	15
Age (years)	42.67 (11.78)	47.40 (11.76)
Sex (% female)	26	11
BMI (kg/m^2)	46.43 (5.78)	44.12 (5.12)
Mean mFD (mm)	0.27 (0.17)	0.29 (0.14)
Maximal mFD (mm)	0.75 (0.34)	0.98 (0.81)
Hypertension (%)	54.55	73.33
Type-1 diabetes (%)	3.03	0
Type-2 diabetes (%)	3.03	0
Smoking (%)	9.09	0

Note: Counts, percentages, or means listed. *SD* is shown in brackets. Sample size for different measures varies, for example, age is available for all participants while not all participants provide MRI data and, hence, mean framewise displacement (mFD) values at baseline.

2.5.4 | Functional decoding

In an exploratory analysis, we compared the resulting contrast maps with whole-brain activation maps from the NeuroSynth (https://www.neurosynth.org/) database (Yarkoni, Poldrack, Nichols, Essen, & Wager, 2011). We uploaded the contrast images for change BMI and average logmFD on NeuroVault, and applied the decoding classifier. This classifier estimates the similarity of meta-analytic activation maps of +500 search terms with our contrast maps. We reported the three top terms for both contrasts.

3 | RESULTS

Histograms on baseline characteristics revealed that patients in the control group did not differ notably from the intervention group regarding BMI and mFD. There were slight differences in the distribution of sex and age, the control group had a higher number of male participants ($n = 4$ vs. $n = 10$) and a higher mean age (47.14 vs. 39.33). Change in BMI of the MRI sample throughout the study is depicted in Figure 1 (comprehensive table on available BMI data in Supporting Information).

3.1 | Confirmatory analysis (pre-registered)

3.1.1 | Whole-brain analysis

Against our initial hypothesis, there was no interaction effect of group and time point on neither reward network nor DMN functional connectivity in model CA1 (no adjustments). There also was no significant main effect for any of the effects of interest (time, group) in clusterwise inference with FWE-correction. The same was true for models CA2 (adjusting for age, sex, and average of logmFD). Results did not differ between AROMA + CC and AROMA + CC + GSR denoising pipelines. In Model CA3 (adjusting for age, sex, average of logmFD, and baseline BMI), there also was no significant interaction when adding baseline BMI. Yet, we found a significant main effect of time in this model. For AROMA + CC + GSR denoised data, there was decreased functional connectivity of the NAcc with the lateral occipital cortex at baseline compared to follow-up (FWE-corrected $p = .030$), and decreased functional connectivity of the PCC within the DMN to the medial anterior cingulate cortex (FWE-corrected $p = .046$; see Supporting Information). The unthresholded contrast maps of group, time, and group-by-time interaction for the unadjusted model for AROMA + CC + GSR were uploaded on NeuroVault.

3.1.2 | Aggregated functional connectivity analysis

There was no significant group-by-time interaction for aggregated DMN and reward network functional connectivity (see Figure 2 and Supporting Information for a detailed summary of the models), regardless of the adjustments (CA1 without adjustment, CA2 adjusting for age, sex, and average of mFD or CA3 adjusting for age, sex, average of mFD, and baseline BMI), and whether the analyses were performed on two and three time points.

3.2 | Exploratory analysis

3.2.1 | Whole-brain analysis

Reward network functional connectivity was not significantly related to neither average nor change in BMI, for either of the denoising pipelines

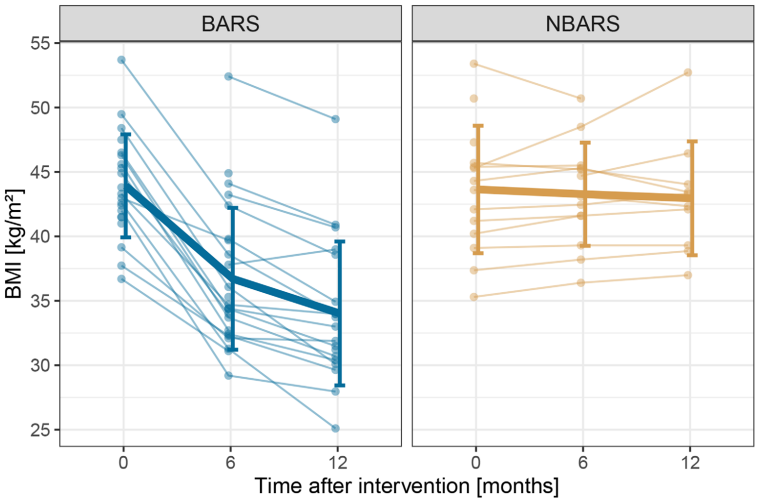

FIGURE 1 Trajectory of BMI separately for the bariatric surgery group (BARS) and the waiting-list control group (NBARS); individual trajectories are plotted in transparent, mean trajectories including standard deviations in opaque colors

implemented in the SwE toolbox implicitly accounts for random effects without the need to specify them through the error term. We used a modified SwE assuming different covariance structures for the intervention and the control group because of their unbalanced sample size. We used an explicit brain mask, derived from the MNI ICBM "152 nonlinear 6th generation" atlas (re-sampled to $3 \times 3 \times 3$ mm^3 and thresholded at 0.5 GM probability) for all analyses. Statistical analyses on the aggregated functional connectivity and imputation of missing data were performed in R version 3.6.1 (Team, 2013).

2.5.1 | Confirmatory analysis (pre-registered)

We tested the pre-registered hypothesis of a time-by-group interaction for two time points.

Whole-brain analysis

As pre-registered, we performed the analysis for baseline and follow-up time points only, for AROMA + CC and AROMA + CC + GSR denoising pipelines and adjusting for no confounders (model CA1), age, sex, and average logmFD of both time points (model CA2) and age, sex, average logmFD, and baseline BMI (model CA3). Because the information about the BMI at baseline of one participant in the intervention group was missing, we employed multivariate imputation to replace this value, for details see Supporting Information.

Aggregated functional connectivity analysis

We analyzed the aggregate functional connectivity (aggFC) using linear mixed models in the R package lme4 (Bates, Sarkar, Bates, & Matrix, 2007). We deviated from the pre-registration by only investigating data from the AROMA + CC + GSR denoising pipeline. First, we investigated the time-by-group interaction for baseline and follow-up time points only. We adjusted for no confounders (model CA1), either for baseline age, sex, average of logmFD of both time points (model CA2) or additionally for baseline BMI (model CA3). We performed model comparison between R1 and R0 models, where R1 = lmer(aggFC ~ timepoint*group + age + sex + [1|subj]), and R0 = lmer(aggFC ~ timepoint + group + age + sex + [1|subj]). As specified in the pre-registration, we repeated the above-mentioned interaction analysis for all three time points.

2.5.2 | Exploratory analysis

Whole-brain analysis

As described in the pre-registration, we calculated the between- and within-subject centered values of BMI (Guillaume et al., 2014). This model, containing average BMI and BMI change, allowed us to disentangle the differential effects of these variables on functional connectivity. We first estimated their effects in a model adjusting for baseline age and sex (Model EA1) and then additionally controlling for logmFD (Model EA2). As we previously reported correlated change in BMI and head motion in this sample (Beyer et al., 2019), we explored a refined model including average BMI and logmFD and change in both measures, along with baseline age and sex (Model EA3). Here, we aimed to see whether any effect of change in BMI would be detectable when adjusting for the change in head motion. In addition to these pre-registered exploratory analyses, we explored our whole-brain group-by-time point interaction models for the data of all three time points on whole-brain level and for aggregated values. In this model, time was represented as factor taking into account possible nonlinear time courses in the increase and decrease of functional connectivity over the course of 1 year, which may occur depending on the phase of weight management (Olivo et al., 2017). The resulting factorial design contained one regressor for each time point per group (see Supporting Information for depiction of design matrix). This analysis had not been pre-registered. Here, we used individual logmFD values (not averaged) as covariate to capture variance in logmFD change over time points. We investigated two models adjusting for age and sex (Model EA4) and age, sex, and logmFD (Model EA5). For a better understanding of the unique contribution of average and longitudinal change in logmFD measures, we tested the association of head motion and functional connectivity (FC) in the additional exploratory Model EA6: FC = between-subject logmFD + within-subject logmFD with age and sex as nuisance covariates.

Aggregated functional connectivity analysis

Further, we performed the pre-registered exploratory analysis with average BMI and change in BMI as predictors of the aggregated functional connectivity from AROMA + CC + GSR denoised data of both networks. We calculated three models with average and change in BMI as predictors of interest and adjusted for baseline age and sex (Model EA1), logmFD (Model EA2), and average and change in logmFD (Model EA3).

2.5.3 | Statistical inference

Whole-brain analysis

To ensure robustness of our results, we used nonparametric inference testing based on wild bootstrap with an unrestricted SwE on all contrasts of interest for clusterwise inference. Deviating from the pre-registration, we used Type C2 instead of Type C3 for small sample bias adjustment, as this was recommended for wild bootstraps in the SwE manual. Deviating from the pre-registration but prior to the analysis, we fixed a cluster forming threshold of $p < .001$ for more rigorous multiple comparison adjustment (instead of $p < .01$), and 1,000 bootstraps due to required computation time (instead of 5,000). Significant clusters are defined as family-wise error (FWE) corrected $p < .05$. The anatomical localization of significant clusters was investigated with the SPM Anatomy toolbox, version 2.2c (Eickhoff et al., 2005) and the Harvard-Oxford Atlas in FSL version 5.0.11.

Aggregated functional connectivity analysis

The interaction effect of group and time point in the models of aggregated functional connectivity was considered significant if the model comparison between R1 and R0 models using the anova command showed $p < .05$. In all exploratory models, we considered all coefficients with $p < .05$ as significant.

2.2 | MRI acquisition

MRI was performed with a 12-channel head coil on a 3 Tesla Trio, Siemens (Erlangen) with the syngo B17 software. T1-weighted anatomical images were acquired as described in Prehn et al. (2020) (with MPRAGE, repetition time (TR) = 1900 ms, echo time (TE) = 2.52 ms, flip angle = 9°, voxel size = $1 \times 1 \times 1$ mm^3, 192 sagittal slices). Resting-state echo-planar imaging was acquired with a TR of 2.3 s and TE of 30 ms. The image matrix was 64×64 with an in-plane resolution of 3 mm × 3 mm and 34 slices with a slice thickness of 4 mm. One hundred and fifty volumes were acquired, resulting in a total acquisition time of 5:45 min. Additionally, a gradient echo field map with a TE difference of 2.46 ms was acquired to correct for field in homogeneities. Participants were instructed to close their eyes but to remain awake during scanning.

2.3 | Preprocessing

2.3.1 | Minimal preprocessing

Imaging data analysis was conducted using AFNI 19.1.05, ANTS 2.3.1, FSL 6.0.1 and FreeSurfer 6.0.0p1, wrapped in a nipype workflow (version 1.2.0) in Python 2.7.15 which can be found on https://github.com/fBeyer89/ADI_preproc/. T1-weighted images were first processed by FreeSurfer's cross-sectional pipeline (Fischl, 2012). Then, Freesurfer's longitudinal stream was applied to all cross-sectional runs (Reuter & Fischl, 2011). Here, white matter and cerebral spinal fluid masks were derived based on FreeSurfer's segmentation file for quality control of rsfMRI preprocessing. The skull-stripped brain was then coregistered to the MNI152 $2 \times 2 \times 2$ mm template using ANTS (Avants, Tustison, Song, & Gee, 2009). Minimal functional preprocessing included the removal of first four volumes, motion correction (FSL's MCFLIRT), fieldmap distortion correction (FSL's fsl_prepare_fieldmap and FUGUE) and coregistration to the subject's individual longitudinal anatomical space (FreeSurfer's bbregister). In more detail, the transformations derived from the latter three steps were combined into one and applied in a single step. For further analysis and ICA-AROMA processing, the minimally preprocessed data were intensity normalized and smoothed with a 6 mm Gaussian kernel (fslmaths–kernel gauss 2.548).

2.3.2 | Denoising pipelines

In the pre-registration, we specified two denoising pipelines, ICA-AROMA and CompCor (AROMA + CC) and ICA-AROMA, CompCor and global signal regression (AROMA + CC + GSR), for details, see Supporting Information (Ciric et al., 2017; Parkes, Fulcher, Yücel, & Fornito, 2018).

2.3.3 | Quality assessment

The quality of anatomical images and rsfMRI was assessed separately. To control the quality of the anatomical imaged, FreeSurfer cross-sectional and longitudinal segmentations were visually checked according to Klapwijk, et al. (2019). We excluded five datasets from three participants because of excessive head motion leading to failed pial reconstruction and anatomical–functional coregistration. RsfMRI quality control was performed according to the protocol by Ciric et al. (2018) (see Supporting Information for more details). Head motion was quantified using mean framewise displacement (mFD) according to Power, et al. (2012) and log-transformed for further analysis (logmFD). As pre-registered, we did not exclude anybody based on high average head motion (Beyer et al., 2020).

2.4 | Functional connectivity

2.4.1 | Whole brain functional connectivity

To derive reward network and DMN functional connectivity maps, we used NAcc and PCC/precuneus as seed regions of interest (ROI), respectively. We did not select vmPFC for the reward network due to low SNR. Based on FreeSurfer's segmentation files and Desikan–Killiany parcellation, we created seed masks using mri_binarize (thresholded for NAcc at 26, 58; precuneus at 1025, 2025) and averaged them over hemispheres. Then, we used NiftiLabelsMasker and NiftiMasker to extract the standardized time series from the seed regions and the whole brain. We calculated the Pearson's correlation between them with numpy.dot, performed r-to-z Fisher-transformation and saved the resulting correlation maps for each preprocessing pipeline (minimally preprocessed, AROMA, AROMA + CC, AROMA + CC + GSR). Finally, the connectivity maps were transformed into MNI space using the affine transformation and nonlinear warp derived with ANTS during anatomical preprocessing.

2.4.2 | Aggregated within-network functional connectivity

To extract aggregated within-network functional connectivity, we first calculated the mean DMN and reward network over all participants and time points, adjusted for age and sex. We used GSR-denoised data as input and clusterwise bootstrapping with $N = 1000$. Network masks were formed from all voxels within clusters which survived a clusterwise multiple comparison correction of FWE-corrected $p < .05$. We extracted the average GSR-denoised functional connectivity from these masks.

2.5 | Statistical analysis

Statistical analyses were performed in MATLAB version 9.7.0.1190202 (R2019b MATLAB, 2018) using the SwE toolbox version 2.2.2 (Guillaume, Hua, Thompson, Waldorp, & Nichols, 2014) as implemented in the Statistical Parametric Mapping software (SPM12.7770; Ashburner et al., 2014). The marginal model

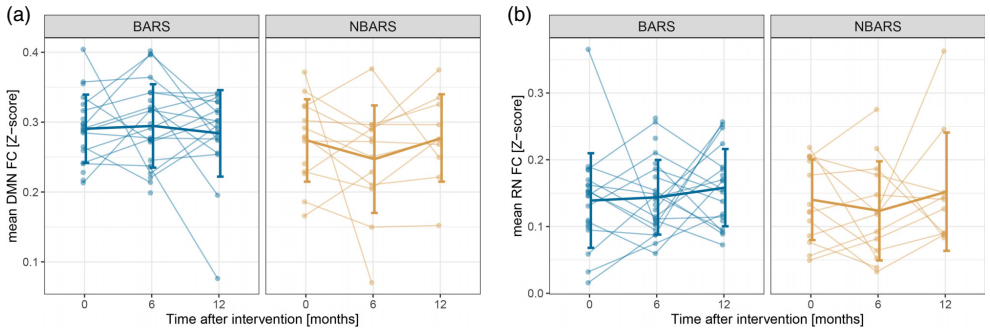

FIGURE 2 Mean network connectivity per group over time separately for the bariatric surgery group (BARS) and the waiting-list control group (NBARS); individual trajectories are plotted in transparent, mean trajectories including *SD*s in opaque colors

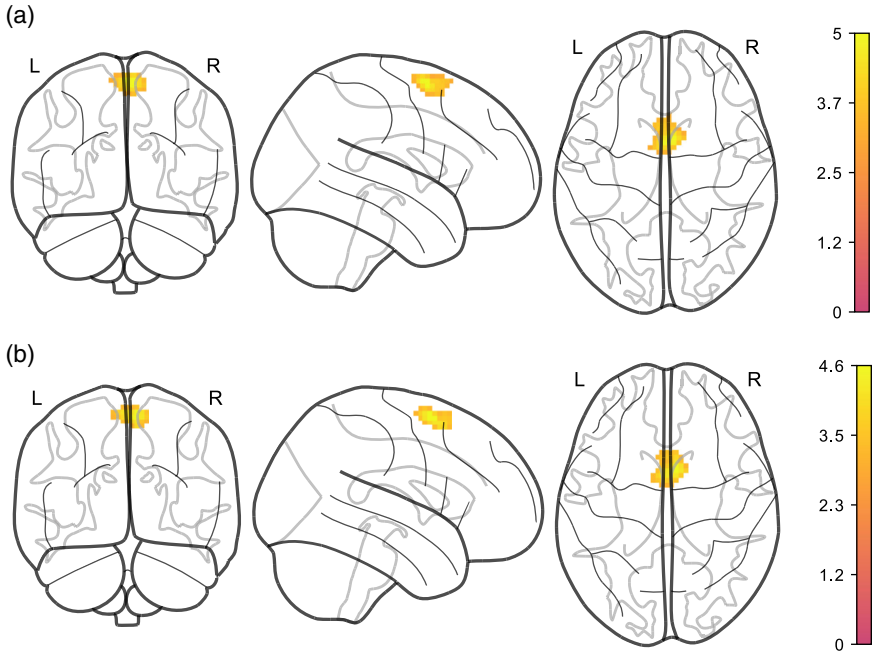

FIGURE 3 Stronger BMI decrease is associated with increased functional connectivity between NAcc and posterior-medial frontal region, adjusted for age, sex, average BMI, and logmFD (Model EA3). (a) denoised with AROMA + CC, (b) denoised with AROMA + CC + GSR. Legends denote empirical *Z* values

and regardless whether we adjusted for logmFD in Models EA1 and EA2. Only in Model EA3 (adjusting for average and change in both BMI and logmFD), we found that more BMI decrease (e.g., weight loss) predicted higher functional connectivity between NAcc and a cluster in the posterior-medial frontal region (see Figure 3 and Table 3).

The peak voxel was classified as belonging to superior frontal gyrus (45% probability) and supplementary motor area (SMA; 37% probability) in the Harvard–Oxford atlas. Voxel activation at local maximum within this cluster was significant at peak level after FWE-correction ($p = .030$), similarly in AROMA + CC + GSR-denoised data ($p = .041$).

Moreover, average logmFD was positively associated with functional connectivity between NAcc and motor cortex in Model EA3 for both denoising pipelines (see Figure 4 and Table 3). For the DMN, we found that higher average BMI predicted lower functional

TABLE 2 Changes in functional connectivity in whole brain analysis in Models EA1 and EA2

		Clusterwise[a]			Voxelwise at local maximum					
						MNI coordinates				
Seed	Covariates	FWE-corr. P	Cluster size	Z score	FWE-corr. P	X	Y	Z	Hem	Anatomical region[b]
Average BMI (decrease)										
PCC (CC)	Age, sex	0.006	212	1.708	0.019	−6	−30	−3		–
					0.045	−3	−45	6		–
					0.056	12	−39	0	R	Lingual gyrus
		0.035	70	1.562	0.129	−48	−9	−15	R	Superior temporal gyrus
					0.287	−54	−3	−21	R	Middle temporal gyrus
		0.032	75	1.573	0.173	−3	57	−12	L	Mid orbital gyrus
					0.199	9	54	−6	R	Mid orbital gyrus
		0.030	77	1.578	0.299	60	−12	−6	L	Middle temporal gyrus
					0.514	66	−21	−9	L	Middle temporal gyrus
Average BMI (decrease)										
PCC (CC)	Age, sex, log mFD	0.002	230	1.772	0.014	−6	−30	−3		–
					0.051	−3	−45	6		–
					0.075	12	−39	0	R	Lingual gyrus
		0.044	70	1.602	0.146	−51	−9	−12	L	Mid orbital gyrus
					0.308	−54	−3	−21	R	Mid orbital gyrus
		0.040	76	1.617	0.185	−3	57	−12	L	Superior temporal gyrus
					0.249	9	54	−6	L	Middle temporal gyrus
		0.047	67	1.593	0.331	60	−12	−6	R	Superior temporal gyrus
					0.574	66	−21	−9	R	Middle temporal gyrus

Abbreviations: CC, preprocessing with AROMA + CC; FWE-corr., family-wise error corrected; GSR, preprocessing with AROMA + CC + GSR; Hem, hemisphere; L, left; MNI (Montreal Neurological Institute) coordinates of primary peak location: X, sagittal; Y, coronal; Z, axial; R, right.

[a]To identify significant clusters, we applied a cluster size threshold with $p < .001$ determined by Wild Bootstrap of 1,000 samples.

[b]Connectivity with maximum three voxels that mark local maxima within the respective cluster; more detailed description of anatomical regions that are assigned to overall clusters and corresponding probability in Supporting Information.

connectivity of the precuneus/PCC with the lingual gyrus, mid orbital gyrus and temporal gyrus in the images denoised with AROMA + CC. This finding was significant in Models EA1, EA2, and EA3 (see Figures 5 and 6 and Table 2). Yet, none of the clusters survived statistical thresholding when using AROMA + CC + GSR denoised data (see Table 3). Unthresholded maps for the *t*-tests as well as contrasts of average BMI and change BMI of the main model, and post hoc contrasts for average logmFD and change in logmFD were published on NeuroVault.

Similarly to the analysis with two time points, there was no significant interaction or main effect when analyzing Models EA4 and EA5 in the full data set of three time points for neither reward network nor DMN.

In the additional exploratory model including only head motion (EA6), higher average logmFD was associated with stronger functional connectivity between the NAcc and a cluster located in proximity to the central sulcus and motor areas (see Table 4 and Figure 7). This cluster only differed in size between denoising pipelines. We did not find any clusters with a significant association of either average logmFD or change in logmFD and DMN functional connectivity.

3.2.2 | Aggregated functional connectivity analysis

As expected, there was no association of average BMI or within-subject BMI change and within reward network functional

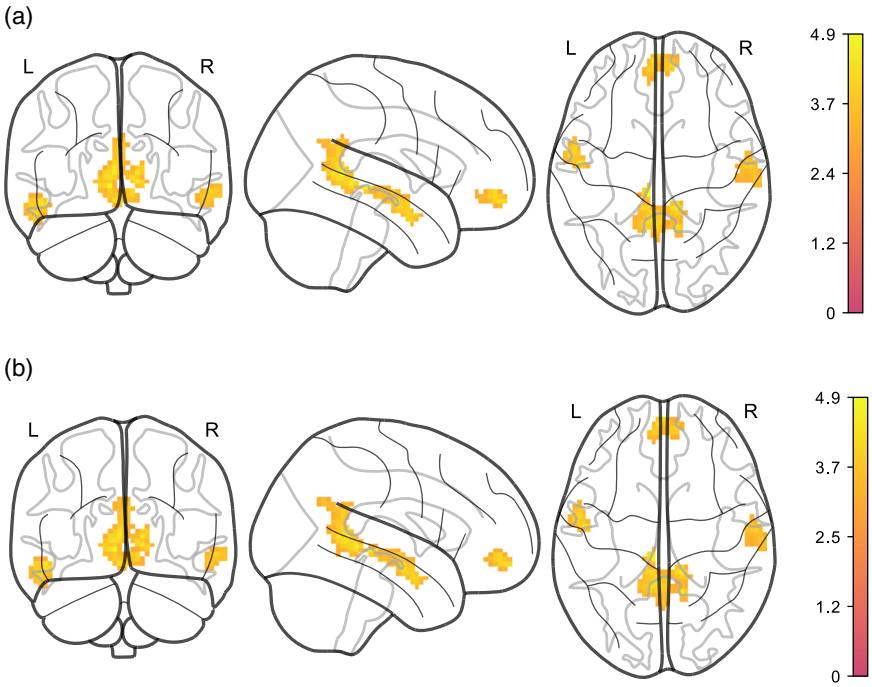

FIGURE 5 Higher average BMI is associated with lower functional connectivity of PCC/precuneus with different regions in AROMA + CC denoised data. (a) adjusted for age and sex (Model EA1). (b) adjusted for age, sex, and logmFD (EA2). Legends denote empirical *Z* values

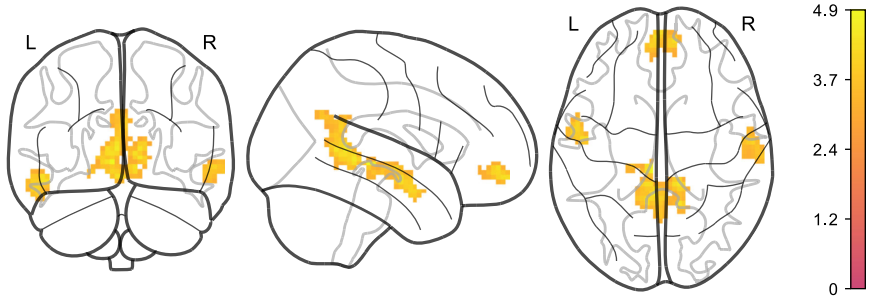

FIGURE 6 Higher average BMI is associated with lower functional connectivity of PCC/precuneus with different regions, adjusted for age, sex, average BMI, average logmFD, and change in logmFD (Model EA3) in AROMA + CC denoised data. Legend denotes empirical *Z* values

functional connectivity between reward network regions to decrease, as bariatric surgery has been previously shown to reduce hyper-activation in reward network regions and hedonic motivation to eat (Cerit et al., 2019; Ochner, Stice, et al., 2012; Scholtz et al., 2013). These studies, notably, did not include adequate longitudinal obese control groups, making false-positive findings possible. We thus conclude that surgery-induced heavy weight loss does not strongly affect DMN and reward network functional connectivity based on the current results.

However, in an exploratory analysis, stronger BMI decrease predicted higher connectivity of the NAcc and a cluster in a posterior-medial frontal brain region. Based on the Harvard-Oxford atlas and

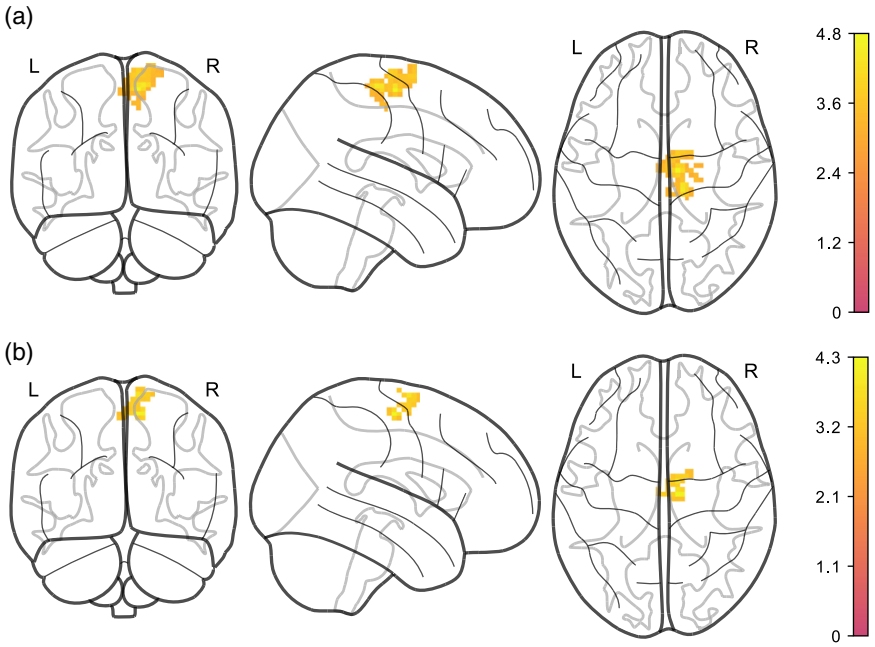

FIGURE 4 Higher average logmFD is positively associated with functional connectivity between NAcc and motor cortex, adjusted for age, sex, average BMI, change in BMI, and change in logmFD (Model EA3). (a) denoised with AROMA + CC, (b) denoised with AROMA + CC + GSR. Note that clusters have different sizes depending on denoising pipeline. Legends denote empirical *Z* values

terms. For the https://neurosynth.org/decode/?neurovault=441783 frontal, anterior insula and inferior frontal were the top terms, while for the https://neurosynth.org/decode/?neurovault=441784, primary motor, motor, and premotor cortex were the meta-analytic activation maps most similar to this contract. The functional connectivity contrasts were thus somewhat distinct, though the decoding method does not allow to conclude specificity (for further information, see here https://www.talyarkoni.org/blog/tag/neurosynth/.

4 | DISCUSSION

In this pre-registered study, we investigated the effects of bariatric surgery on the functional connectivity of major resting-state brain networks in a longitudinal controlled design. Moreover, we explored the longitudinal relationship of surgery-induced weight loss and functional connectivity, and carefully adjusted for head motion by using two efficient denoising pipelines and controlling for head motion on the group level.

We did not detect significant effects of bariatric surgery compared to waiting on whole-brain functional connectivity of the PCC and NAcc, core hubs of the reward network and DMN, according to pre-registered whole-brain analyses. This was regardless of whether we adjusted for age, sex, and individual head motion. DMN and reward network functional connectivity was lower at baseline compared to follow-up for the whole group only when adjusting for age, sex, average logmFD and baseline BMI. In an exploratory model, disentangling the effects of average and change in BMI, higher BMI was associated with lower DMN functional connectivity for the more lenient denoising pipeline. When we additionally adjusted for both, average and change in head motion, decreases in BMI between the three time points were associated with increased connectivity of the NAcc with a posterior-medial frontal cluster. This result was significant in both denoising pipelines. Functional decoding revealed similarities of the connectivity pattern with frontal, anterior insula, and inferior frontal activation patterns. Finally, higher average head motion was associated with increased NAcc connectivity with a cluster in precentral gyrus, close to, yet more posterior cluster associated with change BMI.

In this study, we could not confirm our pre-registered hypotheses. Based on previous studies in bariatric surgery patients, we expected within-DMN functional connectivity to increase, and DMN functional connectivity to other somatosensory and attention networks to decrease, in line with more efficient processing of visceral and bodily signals after surgery (Frank et al., 2013; Li et al., 2018; McFadden, Cornier, Melanson, Bechtell, & Tregellas, 2013). Further, we expected

TABLE 3 Changes in functional connectivity in whole brain analysis in Model EA3

		Clusterwise[a]			Voxelwise at local maximum					
						MNI coordinates				
Seed	Covariates	FWE-corr. P	Cluster size	Z score	FWE-corr. P	X	Y	Z	Hem	Anatomical region[b]
Change in BMI (decrease)										
NAcc (CC)	Age, sex	0.030	112	1.671	0.021	6	6	66	R	Posterior-medial frontal
Average logmFD (increase)										
NAcc (CC)	Age, sex	0.006	143	1.588	0.034	9	−15	60	R	Posterior-medial frontal
					0.094	12	−27	63	R	Paracentral lobule
					0.462	9	−18	72	R	Posterior-medial frontal
Change in BMI (decrease)										
NAcc (GSR)	Age, sex	0.041	99	1.457	0.101	6	9	63	R	Posterior-medial frontal
					0.374	0	3	66	L	Posterior-medial frontal
Average logmFD (increase)										
NAcc (GSR)	Age, sex	0.021	46	1.768	0.134	9	−15	60	R	Posterior-medial frontal
					0.487	9	−6	72	L	Posterior-medial frontal
					0.914	0	−15	60		
Average BMI (decrease)										
PCC (CC)	Age, sex	0.002	251	1.796	0.021	−6	−30	−3		–
					0.052	−3	−45	6		–
					0.067	12	−39	0	R	Lingual gyrus
		0.042	70	1.612	0.128	−51	−9	−12	L	Mid orbital gyrus
					0.273	−54	−3	−21	R	Mid orbital gyrus
		0.021	91	1.658	0.134	−3	57	−12	L	Superior temporal gyrus
					0.152	9	54	−6	L	Middle temporal gyrus
		0.045	69	1.609	0.308	60	−12	−6	R	Superior temporal gyrus
					0.583	66	−21	−9	R	Middle temporal gyrus

Abbreviations: CC, preprocessing with AROMA + CC; FWE-corr., family-wise error corrected; GSR, preprocessing with AROMA + CC + GSR; Hem, hemisphere; L, left; MNI (Montreal Neurological Institute) coordinates of primary peak location: X, sagittal; Y, coronal; Z, axial; R, right.
[a]To identify significant clusters, we applied a cluster size threshold with $p < .001$ determined by Wild Bootstrap of 1,000 samples.
[b]Connectivity with maximum three voxels that mark local maxima within the respective cluster; more detailed description of anatomical regions that are assigned to overall clusters and corresponding probability in Supporting Information.

connectivity in models EA1, EA2, or EA3 adjusting for age, sex, and logmFD (for detailed results, see Supporting Information).

Like in the whole-brain analysis, higher average BMI was associated with reduced aggregated DMN functional connectivity, regardless of whether we adjusted for logmFD (Model EA1: $p = .014$ and EA2: $p = .017$). The association also remained significant when we split logmFD into average and change in logmFD (EA3) ($p = .015$) and there was no significant association of average or change in logmFD with DMN functional connectivity (see Supporting Information for overview of all models).

3.2.3 | Functional decoding

Functional decoding of the two activation patterns from the pre-registered, exploratory analysis EA3 showed different top association

NeuroSynth decoding, this region might be part of the salience network and involved in action preparation. The enhanced functional connectivity between the NAcc and this region seems at odds with our expectation of reduced hedonic drive to eat after bariatric surgery. On the other hand, higher connectivity might also indicate a better crosstalk between hedonic drive and salience processing in action planning. Previously, a decrease in local (regional homogeneity [ReHo] and frequency of low-amplitude oscillations) and global connectivity (degree centrality) measures in a similar region of the left SMA was reported after glucose administration (Al-Zubaidi et al., 2019). Reduced connectivity in this region was interpreted as an inhibition of action planning or initiation because of fulfilled energy requirements and reduced need for foraging. Yet, this lower regional (and global) connectivity might also reflect a relative shift, that is, less connectivity to distributed brain regions, but higher connectivity within the reward-action inhibition network. One could argue that a higher level of segregation (i.e., higher SMA and NAcc connectivity) of signals between the reward network and action initiation regions could relate to more efficient information transfer (Sporns, 2013). Yet, this interpretation is highly speculative, and increased ReHo in motor regions has also been reported after bariatric surgery (Rullmann et al., 2018). Further research thus should address whether the connectivity between NAcc and SMA is a relevant feature in altered brain connectivity after bariatric surgery.

Overall, our results point to the importance of head motion as a confounder in neuroimaging studies in obesity, challenging definite conclusions on the relationship between weight loss and functional connectivity changes. Previously, we reported a decrease in head motion in the bariatric surgery versus control patients in this sample (Beyer et al., 2020), which might be due to weight loss related alterations in breathing patterns or less discomfort in the scanner (Fair et al., 2020; Matos et al., 2012, Beyer et al., in preparation). We, therefore, conducted careful analyses of the impact of head motion on our results. To our surprise, the effect of weight loss on the connectivity of the NAcc with the posterior-medial frontal region was only present when separating average mFD and change in mFD and thereby introducing two instead of one regressor into the model. These results may be due to the presence of multicollinearity between change in FD and change in BMI which might appear more pronounced in the split model, and thus lead to unreliable estimations of effects and standard errors. Contrarily, one could argue that only with the careful disentanglement of average and change in BMI and FD the effect of change in BMI could be singled out. This argument is supported by the survival of the cluster when using AROMA + CC + GSR denoised data, and the distinct results of the decoding analysis. Further, average FD was associated with a cluster in a similar, yet not identical region, and crucially, this association was positive. Thus, confounding of the negative BMI change effect and the positive average head motion effect on posterior-frontal functional connectivity seems unlikely. Head motion also played a role in the association of higher BMI and reduced DMN functional connectivity. While this result was no longer significant on a whole-brain level when using stringent denoising, aggregated within-DMN functional connectivity was negatively associated with BMI in both denoising schemes. Thereby, this result echoes a previous finding from our group, and may be interpreted as accelerated age-related decline of the DMN in relation to the cardiometabolic risk related to BMI. Yet, midline regions are prone to motion artifacts and doubts regarding the complete removal of motion confounding remain (Savalia et al., 2016). The major strength of our study is the prospective intervention controlled design. We compared bariatric surgery patients to an obese control group who did not differ in baseline BMI, comorbidities, treatment history, or recommendation and were scanned after the same time intervals (Thiese, 2014). Another strength of our study was the pre-registered analysis plan, which was corrected prior to statistical analysis after we noticed flaws in the first version. In particular, we included more details on denoising pipelines and models and determined that we would use the SwE toolbox, an advanced statistical toolbox to deal with longitudinal repeated measures (Guillaume et al., 2014). Opposed to the flexible factorial models which is the standard in SPM, marginal models use less degrees of freedom, and thus allow for the inclusion of covariates and higher power.

Limitations of our study include the low number of patients who participated in all three time points. In total, only 34 participants contributed to the estimation of the longitudinal effects with at least two time points. Patients in the intervention group were not missing at random over time points, as often, before surgery, they did not fit into the MRI scanner. While this sample size is comparable to previous rsfMRI studies in bariatric surgery, it seems unlikely that our power was high enough to detect small effect sizes. Increasing the sample size, for example, by pooling data, would increase power to enable analyzing differences between surgery types. Indeed, we did not differentiate due to small sample sizes for each surgery type, yet separate analyses for restrictive (e.g., GB and VSG) and malabsorptive-restrictive surgical interventions (e.g., RYGB) should be subject of future research as they may act differently on metabolism, eating behavior, and glucose control (Buchwald et al., 2004; Hao et al., 2017). Distinct effects on the metabolism could further increase sensitivity for changes in the DMN (Cha et al., 2015). We used seed-based connectivity to derive large-scale brain networks. While this approach yielded reasonable DMN and reward network maps, it is a univariate approach not taking into account the inter-relatedness of subnetworks and assuming that the connectivity of a central hub reflects the connectivity of the network as a whole. Furthermore, our rsfMRI was relatively short, which might have further reduced our power. We did not monitor hunger or satiety in our design, although all participants were scanned after the intake of a breakfast following an overnight fast. Hunger feelings and levels of appetite regulating hormones such as insulin and ghrelin have been shown to predict reward network responsivity to food cues, as well as resting-state brain organization (Kroemer et al., 2012; Lepping et al., 2015; Ochner, Laferrére, et al., 2012; Wiemerslage et al., 2016), and might thus have confounded our results (Li et al., 2019). Size and composition of our sample did not allow sex-stratified analyses. However, the disproportionate sex distribution is reflective of the prevalence differences and under-utilization of bariatric surgery by men (Chooi, Ding, & Magkos, 2019; Fuchs et al., 2015).

TABLE 4 Changes in functional connectivity in whole brain analysis in Model EA6

		Clusterwise[a]			Voxelwise at local maximum					
						MNI coordinates				
Seed	Covariates	FWE-corr. P	Cluster size	Z score	FWE-corr. P	X	Y	Z	Hem	Anatomical region[b]
Average logmFD (increase)										
NAcc (CC)	Age, sex	0.005	126	1.576	0.053	9	−15	60	R	Posterior-medial frontal
					0.266	12	−24	63	R	Posterior-medial frontal
					0.383	9	−18	69	R	Posterior-medial frontal
Average logmFD (increase)										
NAcc (GSR)	Age, sex	0.027	54	1.770	0.138	9	−15	60	R	Posterior-medial frontal
					0.406	9	−6	72	R	Posterior-medial frontal
					0.898	0	−15	60	L	Posterior-medial frontal

Abbreviations: CC, preprocessing with AROMA + CC; FWE-corr., family-wise error corrected; GSR, preprocessing with AROMA + CC + GSR; Hem, hemisphere; L, left; MNI (Montreal Neurological Institute) coordinates of primary peak location: X, sagittal; Y, coronal; Z, axial; R, right.
[a]To identify significant clusters, we applied a cluster size threshold with $p < .001$ determined by Wild Bootstrap of 1,000 samples.
[b]Connectivity with maximum three voxels that mark local maxima within the respective cluster; more detailed description of anatomical regions that are assigned to overall clusters and corresponding probability in Supporting Information.

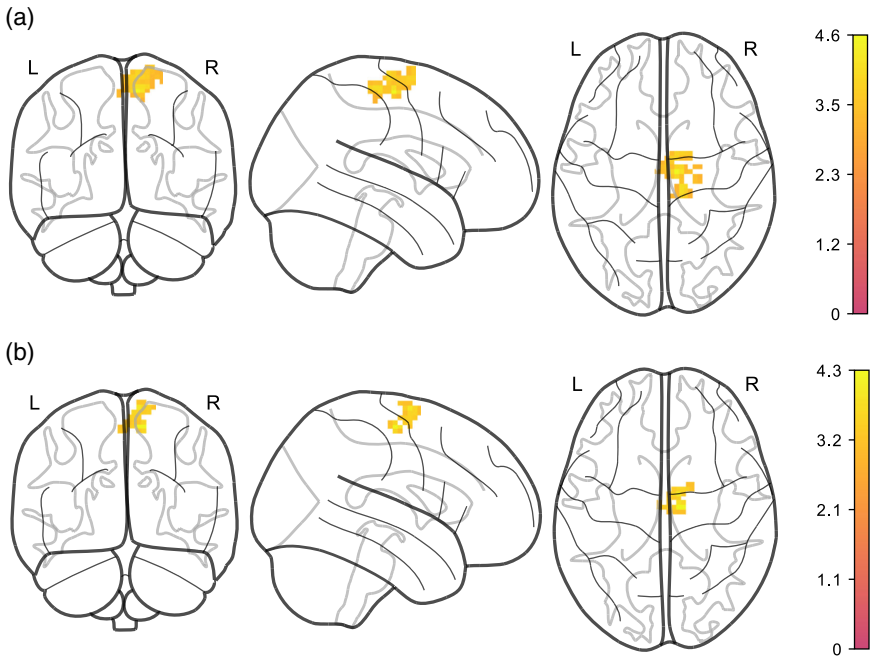

FIGURE 7 Positive association of average logmFD and functional connectivity of NAcc with a cluster in motor cortex, adjusted for age, sex, average BMI, change BMI, and change logmFD. (a) denoised with AROMA + CC, (b) denoised with AROMA + CC + GSR. Legends denote empirical *Z* values

5 | CONCLUSION

Taken together, this prospective well-controlled study did not confirm previous findings claiming strong effects of bariatric surgery on functional connectivity of the reward network and DMN in obese patients. Differential changes in head motion adjustment strongly altered rsfMRI neuroimaging results. We thus recommend to rigorously control head motion at acquisition through online monitoring or prospective motion correction or to investigate brain organization with less motion-prone techniques such as task-based fMRI. Preregistration of concrete and testable hypotheses and publication of null findings as done in the current study would help to increase replicability of the field. Moreover, future studies should include obese control groups, and increase efforts to share and pool valuable patient data into meta-analysis to enhance our understanding of the neural underpinnings of altered gut–brain communication after bariatric surgery.

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CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The raw data that support the findings of this study are available on request from the corresponding author, VW. The data are not publicly available due to privacy/ethical restrictions as the information could compromise the privacy of research participants. Unthresholded contrasts maps uploaded on NeuroVault are accessible under https://identifiers.org/neurovault.collection:9426. Our source code is publicly available. Preprocessing scripts can be found under https://github.com/fBeyer89/ADI_preproc, and analyses scripts can be found under https://github.com/hsx1/adi2_rsfMRI.

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SUPPORTING INFORMATION

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Publication 2

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Gut microbiota link dietary fiber intake and short-chain fatty acid metabolism with eating behavior

Evelyn Medawar[1,2,3]✉, Sven-Bastiaan Haange[4], Ulrike Rolle-Kampczyk[4], Beatrice Engelmann[4], Arne Dietrich[5], Ronja Thieleking[1], Charlotte Wiegank[1], Charlotte Fries[6], Annette Horstmann[1,7,8], Arno Villringer[1,3,9], Martin von Bergen[4,10], Wiebke Fenske[6] and A. Veronica Witte[1,9]

The gut microbiome has been speculated to modulate feeding behavior through multiple factors, including short-chain fatty acids (SCFA). Evidence on this relationship in humans is however lacking. We aimed to explore if specific bacterial genera relate to eating behavior, diet, and SCFA in adults. Moreover, we tested whether eating-related microbiota relate to treatment success in patients after Roux-en-Y gastric bypass (RYGB). Anthropometrics, dietary fiber intake, eating behavior, 16S-rRNA-derived microbiota, and fecal and serum SCFA were correlated in young overweight adults ($n = 27$ (9 F), 21–36 years, BMI 25–31 kg/m^2). Correlated genera were compared in RYGB ($n = 23$ (16 F), 41–70 years, BMI 25–62 kg/m^2) and control patients ($n = 17$ (11 F), 26–69 years, BMI 25–48 kg/m^2). In young adults, 7 bacteria genera, i.e., Alistipes, Blautia, Clostridiales cluster XVIII, Gemmiger, Roseburia, Ruminococcus, and Streptococcus, correlated with healthier eating behavior, while 5 genera, i.e., Clostridiales cluster IV and XIVb, Collinsella, Fusicatenibacter, and Parabacteroides, correlated with unhealthier eating (all $|r| > 0.4$, FDR-corrected $p < 0.05$). Some of these genera including Parabacteroides related to fiber intake and SCFA, and to weight status and treatment response in overweight/obese patients. In this exploratory analysis, specific bacterial genera, particularly Parabacteroides, were associated with weight status and eating behavior in two small, independent and well-characterized cross-sectional samples. These preliminary findings suggest two groups of presumably beneficial and unfavorable genera that relate to eating behavior and weight status, and indicate that dietary fiber and SCFA metabolism may modify these relationships. Larger interventional studies are needed to distinguish correlation from causation.

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BACKGROUND

Gut microbes modulate brain function and behavior via immune, endocrine, neural, and humoral routes [1]. This could play a key role in neuronal feeding circuits and overeating, as dysbiosis of the microbiota composition has been documented in psychiatric eating disorders [2] and obesity [3].

However, nutrition- or body weight-related microbial changes and their functional relevance are still relatively unclear. In mice, gastric bypass-related differences in the microbiota profile, such as a higher abundance of the genera *Escherichia (*phylum *Proteobacteria)* and *Akkermansia (*phylum *Verrucomicrobia)*, induced weight loss when transferred to germ-free animals [4]. In humans, bariatric surgery similarly led to higher overall microbiota diversity and to higher abundance of the species *Escherichia coli* and in some studies to further abundance changes within the phylum *Bacteroidetes*, such as a higher post-surgery ratio of the genera *Bacteroides to Prevotella* [5] and less *Firmicutes* (phylum level) or to more *Gammaproteobacteria* (class level) [6]. The ratio of *Bacteroides to Prevotella* at baseline predicted dietary weight loss success after 24 weeks in an intervention study in 80 overweight individuals [7]. Further, a one-week dietary intervention trial in 20 individuals found that microbial composition predicted glycemic response [8].

Human-to-mouse fecal transplant experiments further underline the causal role of specific microbiota to facilitate weight loss [9], and human-to-human fecal microbiota transplantation (FMT) experiments increased insulin sensitivity according to [10]. In a recent human study, accompanied by mouse model data, an individual's microbiota profile, extracted from fecal samples during periods of dietary weight loss, prevented weight regain when transferred back to the same individuum orally, known as autologuos FMT [11].

Mechanistic insights into how specific gut bacteria modulate human eating behavior and weight status are still limited. The gut microbiota is supposed to affect the host's metabolism by altering energy extraction from food, and by modulating dietary or host-derived compounds that modify the metabolic pathways of the

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host [12]. For example, short-chain fatty acids (SCFA) are excreted by certain gut bacteria as a result of carbohydrate fermentation, and SCFA stimulate the secretion of anorexigenic hormones, such as peptide YY (peptide tyrosine tyrosine or PYY) and glucagon-like-peptide-1 (GLP-1) in the colon, which further signal to hypothalamic nuclei as one mechanism of homeostatic regulation [13]. SCFA can also cross the blood–brain barrier and act as signaling molecules in the brain to directly modulate appetite and food-decision making [1]. First interventional studies showed that intake of butyrate (one type of SCFA) or the butyrate-producing bacteria *Akkermansia spp*. exert beneficial effects on body weight depending on treatment intention in humans [14] and on brain functions in mice [15], including reduced food intake [16]. Notably, specific pre-biotic nutrients, such as dietary fibers, are known to nourish SCFA-producing bacteria in the gut, rendering diet a potent modifier of gut–brain signaling [17].

In sum, the gut microbiome may influence feeding behavior, e.g., by modulating reward and homeostatic signaling [18, 19] and by stimulating the vagal nerve [20], in particular in dysregulated biological systems, such as in food addiction [21] or eating disorders [2]. Yet, direct knowledge if specific genera are linked to eating behavior via dietary intake and SCFA in humans is lacking. Here, we asked whether gut microbial diversity and genera abundance relate to eating behavior, and to SCFA metabolites in the colon (feces) and in the periphery (blood) in a homogenous sample of young overweight adults. In addition, we tested whether the abundance of microbiota that related to eating behavior in that overweight sample correlate with weight status, eating behavior, and treatment success (i.e., achieved weight loss) in another sample, i.e., patients at two years after bariatric surgery and control overweight/obese patients.

METHODS

Samples characteristics and data collection

We included all participants with available microbiota datasets measured at a cross-sectional timepoint from two studies. Sample 1 comprised 27 healthy young overweight adults (9 F, 21–36 years, BMI 25–31 kg/m^2) drawn from a randomized clinical trial (Clinical Trials registration NCT03829189), where baseline data was available from ongoing data collection until January 2021. All participants were included if following a typical Western omnivorous diet and thoroughly screened for habitual dietary patterns (exclusion criteria were assessed via an interview at pre-screening included any sort of restrictive diet (incl. vegan, vegetarian, gluten-free, lactose-free, food allergies), regular excessive caffeine intake (more than 6 cups a day), regular alcohol intake (>1.25 L beer/day or equivalent) or smoking >10 cigarettes/day). Estimated nutrient intake represents a Western style omnivorous diet (10.4 ± 3.6 g/day/1000 kcal), with lower than recommended fiber intake (intake recommendations by WHO and EU nutritional agencies state >25 g or 25–35 g of dietary fiber per day are required to meet healthy intake levels). For further information on dietary and coffee intake see SI (see *Dietary Intake*).

Sample 2 comprised 23 patients two years after Roux-en-Y gastric bypass (RYGB) surgery (see below; "good responders": $n = 11$ (7 F), 41–70 years, BMI 25–29 kg/m^2; "bad responders": $n = 12$ (9 F), 31–67 years, BMI 41–62 kg/m^2), as well as age-, gender- and BMI-matched controls (overweight: $n = 8$ (5 F), 41–58 years, BMI 25–29 kg/m^2; obese: $n = 9$ (6 F), 26–70 years, BMI 41–48 kg/m^2), drawn from an observational study where data collection was completed (ethics proposal 027/17-ek). To compare non-surgery but BMI-matched microbial diversity with post-surgery only datapoints, body weight-matched control groups were recruited and included for microbial analysis.

All participants donated feces (see SI) for microbiota analysis (Shannon effective [22] and relative abundance of microbiota genera), underwent anthropometric measurements, and filled in questionnaires to quantify eating behavior traits. Also, data on dietary fiber intake, hunger ratings after a standardized meal, and SCFA in blood and feces were available in sample 1 (see below).

Microbiota assessment

To assess microbiota community structure we used 16 S rRNA gene profiling of the fecal samples. Therefore, DNA was extracted and V3-V4 variable regions of the 16 S rRNA genes were amplified by PCR and a library was constructed, followed by paired-end 2x250bp Illumina sequencing. These analyses were done by GENEWIZ Germany GmbH, Leipzig. Next, the inhouse Galaxy server using a pipeline implemented with the DADA2 R package processed raw data in fastq format. For each sample, paired-end reads were joined, low-quality reads were removed, reads were corrected, chimeras removed, and Amplicon Sequence Variants (ASVs) were obtained. Taxonomy was annotated to the ASVs using the RDP database [23]. The read counts per ASV with taxonomic annotation were normalized and relative abundances of each ASV and taxa were calculated using the R scripts Rhea. Visualization of all library-indexed genera was done as in [24] by inhouse written R-tools using ggplot2.

Eating behavior

To characterize eating behavior traits, questionnaires based on self-report were used: the Three-Factor Eating Questionnaire (TFE-Q) (German version, [25]) and the Eating Disorder Examination Questionnaire (EDE-Q) (German version, [26]) as available for sample 1 and sample 2, respectively. The TFE-Q assesses three domains of eating behavior (cognitive restraint, disinhibition, hunger), and the EDE-Q covers the subscales dietary restraint, eating concern, weight concern, and shape concern. Scoring was performed according to the respective manuals.

Additional analyses in sample 1

From all measurements available in sample 1 in the context of the RCT (see above), we additionally considered all available hunger ratings after a standardized meal (3 out of 4 measures, 1 with missing data) and all available dietary fiber intake data (from a quantitative food frequency questionnaire, fiber in g/day and fiber per 1000 kcal). We further considered anthropometric assessments to be of interest in this study and limited those to two major health indicators, i.e., systolic blood pressure (mean of three consecutive measurements) and relative body fat (%) obtained from bioelectrical impedance analysis (see SI). Blood was obtained in fasting state (12 ± 3 h fasted) and samples were centrifuged at 3500 revolutions per minute at 7 °C for 6 min. Serum was aliquoted within 1 h of obtainment. Processed aliquots were stored at −80 °C until data analysis. For SCFA in blood and stool, analyzed according to [27], we focused on three major and most abundant SCFAs out of eight measured, i.e., acetate, butyrate, and propionate (see SI). All other measures were not considered of interest to the current analyses.

Obesity surgery in sample 2

For sample 2, RYGB (see SI) patients were selected for microbiota analysis based on their response to the surgical treatment. Specifically, RYGB patients were identified from the database of the University of Leipzig if their surgery dated back at least 2 years and all those were further divided in percentiles according to pre-defined relative excessive weight loss (EWL) thresholds defined more conservatively than previous literature (most common <50% EWL at 18 months, according to [28]. This resulted in 23 RYGB patients good responders: sustained EWL > 70%, mean 93% ± 4 SD, range 86–98%, $n = 12$; bad responders: sustained EWL < 40%, mean 20% ± 13 SD, range 3–35%, $n = 11$). Next, obese and overweight control patients were selected from the database based on age, sex, and BMI to match those two groups of RYGB patients. Afterwards, RYGB patients only filled in a series of questionnaires, performed cognitive tests, and donated blood for another study purpose; and fecal samples of all patients were analyzed. From this dataset, we considered of interest to the current analysis the following variables: weight loss after surgery (in kg and in BMI), all available eating questionnaire data (four EDEQ scales, see above), and microbiota genera abundances based on 16 S rRNA sequencing.

Statistical analysis

Correlational analysis. Relative taxa abundance (%) on the genera level was used as primary variables of interest. Non-normally distributed variables were log- or Tukey-transformed, so that skewness of <|1| was reached (for details Supplementary Fig. 1). No observations were eliminated, instead all cases with microbiota data were complete and included. For the main analysis, 20 out of 121 genera were included as they appeared in at least 80% of individuals [29] and fed into a correlation matrix with all variables of interest in sample 1 (37 variables in total, see above), i.e., Shannon index, 3 TFEQ traits, 3 hunger ratings, body fat, systolic blood pressure, dietary fiber intake (g/day and g/1000 kcal), and 3 SCFA each in feces and blood, respectively. All values were FDR-corrected

Table 1. Descriptives for sample 1.

	Sample 1			
n, sex/gender (F/M)	27 (9 F/18 M)			
	mean	*SD*	*minimum*	*maximum*
age (years)	28.4	4.5	21	36
education (SES index) (score from 3 to 21) (four NAs)	15.0	2.8	8.2	19.2
BMI (kg/m2)	27.7	1.7	25.0	31.2
TFEQ cognitive restraint (sumscore)	5.6	4.1	0	13
TFEQ disinhibition (sumscore)	6.0	2.1	2	11
TFEQ hunger (sumscore)	5.0	3.4	0	12
time fasted (h)	12.5	2.7	6	18
hunger 15 min postprandial (1–8 scale)	4.2	1.7	1	7
hunger 40 min postprandial (1–8 scale)	5.3	1.3	2	7
hunger 65 min postprandial (1–8 scale)	5.3	1.4	2	8
mean systolic blood pressure (mmHg)	128.0	10.9	107.0	152.7
% fat mass (female, male)	34.7 (F) 22.8 (M)	4.2 (F) 5.2 (M)	27.3 (F) 7.6 (M)	39.8 (F) 30.7 (M)
habitual fiber intake / 1000 kcal / d (g)	10.4	3.6	4.4	20.0

and statistical significance was set to $p < 0.05$. Those genera that were significantly associated with eating behavior (TFEQ traits and/or hunger ratings, p-FDR < 0.05) were then correlated with weight status and RYGB treatment success in sample 2. Group differences across overweight, obese, good and bad RYGB responders were tested with non-parametric Kruskal–Wallis tests. Further correlations were tested with Pearson's correlation coefficient *r* for normally distributed variables or with Spearman's rho for non-normally distributed variables. Explorative analysis considerations were addressed according to [30] (see Additional SI).

To further investigate, if the interplay of correlated genera—rather as a holobiont than individually—is determinative of the observed relations, the relation between correlated to non-correlated genera was computed by three composite scores (1)-(3).

$$positive\ sumscore(\%) = relative\ abundance(Alistipes + Blautia + Clostridium\ XVIII + Gemmiger + Roseburia + Ruminococcus + Streptococcus) \quad (1)$$

$$negative\ sumscore(\%) = relative\ abundance(Clostridium\ IV + Clostridium\ XIVb + Collinsella + Fusicatenibacter + Parabacteroides) \quad (2)$$

$$composite \sum score(\%) = (1) - (2) \quad (3)$$

Mediation analysis. Using simple mediation analysis using medmod (https://cran.r-project.org/web/packages/medmod/index.html) in RStudio version 3.6.1, we checked for statistical mediation in sample 1 for variables showing bivariate correlations in the following paths:

i. fiber —> correlated genera or sumscores —> eating behavior (TFEQ, hunger ratings)
ii. eating behavior (TFEQ, hunger ratings) —> fiber —> correlated genera or sumscores
iii. correlated genera or sumscores —> SCFA —> eating behavior (TFEQ, hunger ratings)

Significance was set to $p < 0.05$, and the main analysis for sample 1 was corrected for multiple testing using the false-detection rate (FDR)-correction. All analyses were performed in RStudio version 3.6.1.

RESULTS

Characteristics of sample 1 and 2 are listed below (see Tables 1–2). Data from post-RYGB patients was on average collected 4.7 ± 1.4 years after surgery. Eating behavior traits varied across both samples, and in sample 2, restrained eating and shape/weight concerns differed between those that achieved long-term excessive weight loss after bariatric surgery compared to those that did not (good vs. bad responders, all $W > 58.5$, $p < 0.001$, Table 2, Supplementary Fig. 2).

Overall microbiota diversity at the phylum level was relatively comparable across participants of samples 1 and 2 except higher ratio of Firmicutes to Bacteroidetes in sample 1, and Prevotellaceae and Fusobacteriaceae families were more abundant in patients after RYGB surgery (Fig. 1, Supplementary Figs. 3–4, see SI for details). Additionally, we tested for sex/gender-specific differences in alpha diversity in sample 1 and found none (sample 1: male ($n = 18$) 111 ± 15, female ($n = 7$) 110 ± 13, $t(13) = -0.08$, $p < 0.94$). Due to limited sample size we refrained from further sex-segregated analyses, yet we encourage future meta-analyses to include our datasets (see open data).

Microbiota, eating behavior traits, and health indicators in overweight adults

In sample 1, effective Shannon index as a measure of alpha diversity was included into the main correlation analysis. Almost no correlation with eating behavior was significant, except that higher alpha diversity was significantly associated with 10 min-postprandial hunger ($r = 0.59$, $p = 0.005$). Further, higher relative abundance of *Collinsella* (phylum Actinobacteria), *Clostridium* IV and XIVb, *Fusicatenibacter* (all three phylum Firmicutes), and *Parabacteroides* (phylum Bacteroidetes) were related to less healthy eating behavior (higher TFEQ scores and/or higher hunger ratings, all $0.61 < |r| > 0.42$, p-FDR < 0.05, Fig. 2A). Contrastingly, higher relative abundance of the microbial genera *Alistipes* (phylum Bacteroidetes), *Blautia*, *Clostridium* XVIII, *Gemmiger*, *Roseburia*, *Ruminococcus*, and *Streptococcus* (all phylum Firmicutes) correlated with healthier eating behavior (all $0.76 < |r| > 0.42$, p-FDR < 0.05, Fig. 2B, Supplementary Fig. 5).

Further, *Collinsella* abundance significantly correlated with higher body fat mass (sex-standardized, $r = 0.61$, $p < 0.001$, Fig. 2C). *Streptococcus* abundance was significantly correlated with lower mean systolic blood pressure ($r = -0.70$, p-FDR < 0.001, Fig. 2D).

Relation to dietary fiber intake and SCFA

Out of the 12 genera that were significantly associated with eating behavior (from now on called "(inversely) health-related" genera), three were associated with lower (*Collinsella* and *Parabacteroides*) or higher (*Clostridium XVIII*) dietary fiber intake (all $0.73 < |r| > 0.49$, p-FDR < 0.05, Fig. 3A–C). Moreover, higher dietary fiber intake per se was significantly associated with lower disinhibited eating

Table 2. Descriptives for sample 2.

	Overweight				Obese				Good responders				Bad responders				Group comparison
n, sex/ gender (F/M)	8 (5 F/3 M)				9 (6 F/3 M)				11 (7 F/4 M)				12 (9 F/3 M)				F/t, p
	mean	*SD*	*minimum*	*maximum*	*mean*	*SD*	*minimum*	*maximum*	*mean*	*SD*	*minimum*	*maximum*	*mean*	*SD*	*minimum*	*maximum*	*4 groups / RYGB only*
age (years)	53	4.3	44	58	54	14.8	26	69	51.9	9.4	41	70	54.1	11	31	67	**$W = 1.83$, $p = 0.61$**
BMI (kg/m2) (pre-surgery)	–	–	–	–	–	–	–	–	45.5	7.2	34.6	61	52.7	6.6	41.6	63.6	**$W = 4.74$, $p = 0.03$**
BMI (kg/m2) (>2 years post-surgery)	27.0	1.1	25.9	29.2	45.0	2.7	41.5	47.8	26.3	0.9	25.1	27.9	47.2	6.4	41	61.9	**$W = 28.6$, $p < 0.001$**
time post surgery (months)	–	–	–	–	–	–	–	–	51.3	15.1	25.7	74.2	55.42	18.5	25.3	76.2	**$W = 105$, $p = 0.54$**
EDEQ restraint (mean score)	–	–	–	–	–	–	–	–	0.46	1.1	0	3.6	2.1	1.5	0	5	**$W = 72.5$ $p = 0.003$**
EDEQ eating concern (mean score)	–	–	–	–	–	–	–	–	0.26	0.3	0	0.6	0.9	0.9	0	3	**$W = 84.5$, $p = 0.043$**
EDEQ weight concern (mean score)	–	–	–	–	–	–	–	–	0.56	1	0	3.2	3.3	1.1	1.4	5	**$W = 60$, $p < 0.001$**
EDEQ shape concern (mean score)	–	–	–	–	–	–	–	–	1.1	1	0	3.3	4.2	1.1	1.5	5.5	**$W = 58.5$, $p < 0.001$**

($r = -0.58$, p-FDR < 0.01) and lower body fat mass ($r = -0.75$, p-FDR < 0.0001, Fig. 3D–E).

SCFA concentrations in feces were highly variable and up to ~1000 times higher compared to serum for all three measured SCFA (all $t(24) > 11.6$, $p < 0.001$). Serum acetate was 2.5 times higher compared to butyrate and propionate in serum (Supplementary Table 1).

We observed that higher abundance of some of the inversely health-related genera correlated with higher levels of different SCFA in feces and serum (all $r > 0.50$, p-FDR < 0.01). In addition, most health-related genera correlated with some feces and serum SCFA markers, however revealing both positive and negative associations (only those associated with eating behavior were considered, all $0.65 < |r| > 0.44$, p-FDR < 0.05, Supplementary Fig. 6). Note, that some genera showed differential correlations within the different SCFA, e.g., higher *Alistipes* correlated with higher acetate in both feces and serum and with fecal butyrate, but with lower fecal propionate. Moreover, considering the inversely health-related genera, *Fusicatenibacter* and *Parabacteroides* correlated significantly with higher fecal concentrations of propionate and acetate, respectively.

Also, higher fecal propionate levels correlated significantly with higher cognitive restraint eating ($r = 0.50$, p-FDR = 0.014, Fig. 4A). Higher fecal acetate, butyrate and propionate levels correlated with higher hunger ratings (all $r > 0.45$, all p-FDR < 0.04), but also serum propionate with hunger ($r = 0.45$, p-FDR = 0.03). Moreover, serum acetate and butyrate were inversely associated with body fat mass (all $r > -0.43$, all p-FDR < 0.04) (Fig. 4B–C). Notably, serum levels did not correlate with fecal SCFA concentrations (all $r < |0.17|$, all p-uncorr <0.86, Supplementary Fig. 7).

Genera sumscore and mediation analyses

The negative sumscore of the five inversely health-related genera abundances resulted in significant correlations for two of the eating traits (cognitive restraint $r = 0.59$, p-uncorr = 0.001; disinhibition $r = 0.65$, p-uncorr <0.001, Fig. 5A–B). The positive sumscore of the seven health-related genera abundances showed no significant associations (all p-uncorr <0.95, Supplementary Fig. 8). Neither sumscore correlated with fecal or serum SCFA levels.

Exploratory mediation path analyses of the proposed models did not show statistically significant mediating paths for differences in diet, eating behavior or hunger ratings through differences in *Parabacteroides* or positive/negative sumscores (Supplementary Tables 2–3, Supplementary Fig. 9). Considering SCFA, similar results emerged, except for acetate: here, while the direct effect c′ did not reach significance ($ß = -0.3$, $p = 0.13$), higher *Parabacteroides* abundance was linked with higher post-prandial hunger ratings through higher fecal acetate levels (indirect effect, a*b, $ß = 0.36$, 95% CI [0.05 0.66], $p = 0.02$, Supplementary Table 4).

Exploratory analysis based on reviewer suggestions showed that, when adjusting the correlational analysis for body fat mass, associations with inversely health-related bacterial genera remained largely significant (TFEQ and *Clostridium XlVb*, *Collinsella*, *Fusicatenibacter*, *Parabacteroides*, all $p < 0.05$), yet positively health-related correlations do not (only for hunger ratings with *Clostridium XVIII* and *Roseburia*, all $p < 0.05$) (relating to Fig. 2, for details see SI Table 5). For fiber intake associations, only the negative association with *Collinsella* abundance and TFEQ disinhibition scores remain significant (relating to Fig. 3, for details see SI Table 5). The association between propionate levels in feces and TFEQ cognitive restraint when adjusted for body fat mass is no longer significant (relating to Fig. 4).

Microbiota genera differences between overweight, obese, and surgery groups

In sample 2, we aimed to confirm links between the genera of interest from sample 1 and treatment success and eating

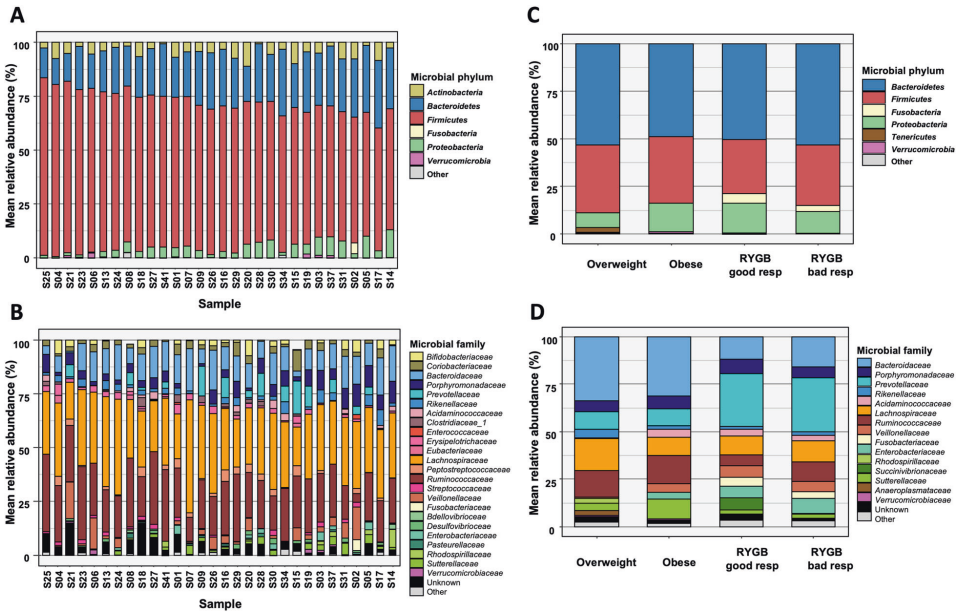

Fig. 1 Microbiota profiling of two cross-sectional cohorts. A Relative abundances of phyla per subject across sample of young, overweight adults (sample 1). Sorted by Firmicutes abundance. **B** Relative abundances of family per subject across sample of young, overweight adults (sample 1). **C** Relative abundances of phyla per group for overweight and obese adults and good and bad responders after RYGB (sample 2). Colors are as in panel A. **D** Relative abundances of family per group for overweight and obese adults and good and bad responders after RYGB (sample 2). Colors are as in panel B.

behavior. Two of the five inversely health-related genera were significantly different between groups (all H(3) >9.5, $p < 0.023$) with lower relative abundance of *Parabacteroides* in good vs. bad responders ($H(1) = 4.9$, $p = 0.027$) Fig. 6A). In addition, six of the seven health-related genera were more abundant in the overweight group (all H(3) >8.3, $p < 0.036$, Fig. 6B), but did not differ in the good vs. bad RYGB responders.

Considering the sumscores, we found that both sumscores differed between groups (Fig. 6C–D, all H(3)>11.3, $p < 0.01$) with the negative sumscore showing higher values in the bad vs. good RYGB responders ($H(1) = 2.1$, $p = 0.036$). In addition, both the positive (n.s.; $H(1) = 1.9$, $p = 0.05$) and the negative sumscore ($H(1) = 2.02$, $p = 0.043$) showed higher values in overweight vs. obese participants.

Bad vs. good RYGB responders showed higher eating restraint scores ($H = 5.3$, $p = 0.022$, Supplementary Fig. 1), and higher scores correlated with higher *Parabacteroides* abundance in these groups ($r = 0.44$, $p = 0.039$, Fig. 6E). Moreover, lower *Parabacteroides* abundance correlated significantly with higher weight loss after surgery ($r = 0.49$, $p = 0.019$, $n = 20$, Fig. 6E). The negative sumscore correlated with unhealthier eating behavior (mean of all EDEQ subscales, $r = 0.47$, $p = 0.027$; EDEQ restraint, $r = 0.49$, $p = 0.022$) and with less weight loss after surgery (Fig. 6E, weight, $r = 0.53$, $p = 0.011$, BMI, $r = 0.53$, $p = 0.011$).

Potential confounders of the gut microbiome

Besides body fat mass, several confounding factors have been proposed to influence gut microbiota, such as time of day of stool collection [31], seasonality [32], coffee consumption [33], and others. Note that statistical tests showed no significant associations of the above mentioned confounders on alpha diversity in our analysis (Table 3). Influences of medication was not tested further, since medical products varied largely in sample 1 and was quite similar across patient groups in sample 2.

DISCUSSION

Combining data from two human cross-sectional datasets, this exploratory analysis finds two groups of microbiota genera that were either positively or inversely associated with both healthier eating behavior and anthropometrics (1) in a deeply phenotyped sample of young overweight adults and (2) when comparing microbiota observed in (1) in patients showing a good or bad response two years after bariatric surgery with matched controls, respectively. More specifically, in young overweight adults, 7 bacterial genera, i.e., *Alistipes*, *Blautia*, *Clostridium XVIII*, *Gemmiger*, *Roseburia*, *Ruminococcus*, and *Streptococcus*, correlated with healthier eating behavior traits and lower subjective hunger ratings, indicating potential benefits for the host metabolism, while 5 bacterial genera, i.e., *Clostridium IV*, *Clostridium XIVb*, *Collinsella*, *Fusicatenibacter*, and *Parabacteroides*, correlated with unhealthier eating traits and higher subjective hunger ratings. *Collinsella* was further related to higher body fat mass and *Streptococcus* to lower systolic blood pressure. The health-related bacterial genera were also more abundant in the overweight good responder controls, compared to the obese bad responder controls and RYGB-operated patients, while the inversely health-related genera showed a less clear distribution across groups, with *Parabacteroides* being significantly less abundant in good vs. bad RYGB-operated patients. Moreover, relative abundance of *Parabacteroides* as well as a composite score of all inversely correlated genera, were associated with higher eating restraint and with

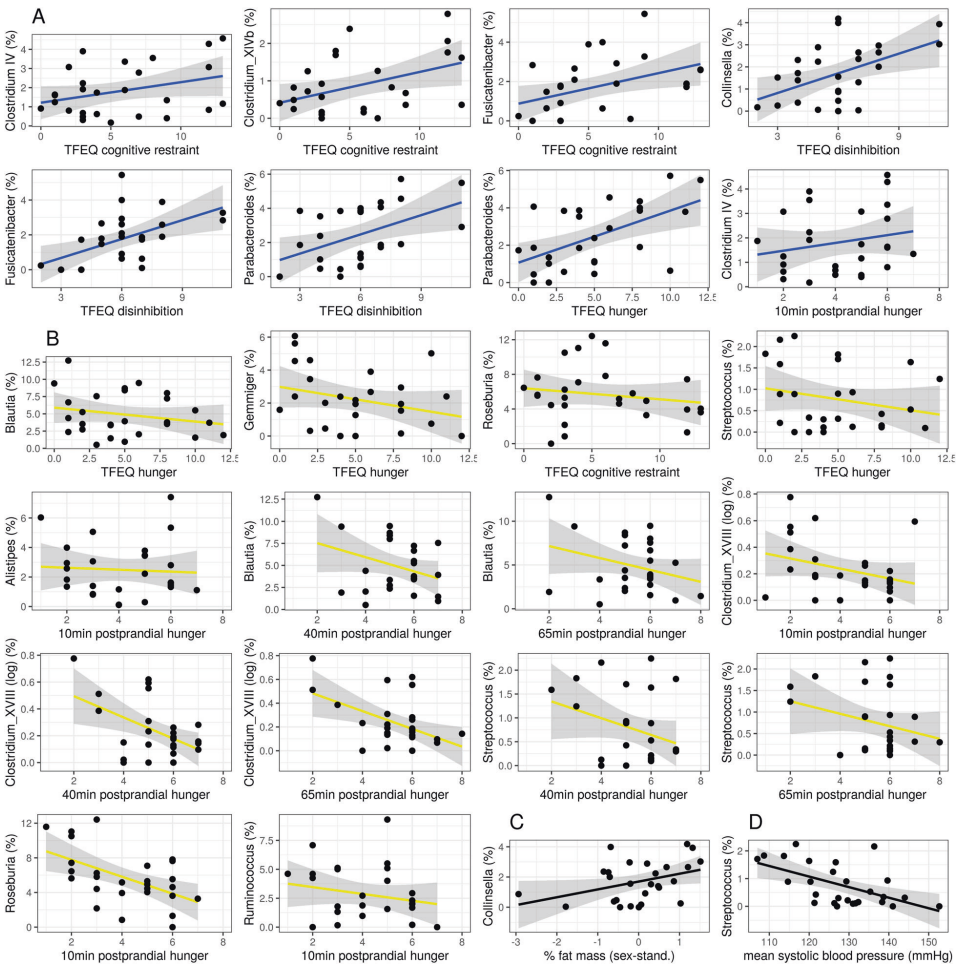

Fig. 2 Pearson's correlations between eating behavior traits (TFEQ and hunger ratings) or health indicators and bacterial genera in overweight adults (all $|r| > 0.42$, all p-FDR < 0.05; sample 1). A inversely health-related genera (blue), **B** health-related genera (yellow), **C** Collinsella and body fat mass (black), and **D** Streptococcus and mean systolic blood pressure (black).

lower post-operative weight loss across both RYGB groups. Considering diet and SCFA-related pathways, we observed that higher dietary fiber intake in overweight adults correlated with more abundant *Clostridium XVIII*, and less abundant *Collinsella* and *Parabacteroides*, as well as with healthier eating behavior and anthropometrics. While SCFA showed a rather mixed pattern of correlations with the different markers, *Fusicatenibacter* and *Parabacteroides* abundance correlated with higher fecal propionate and acetate, respectively, that again correlated with elevated hunger. Contrastingly, higher acetate and butyrate in serum correlated with lower fat mass, indicating a possible inverse association of acetate in feces and serum with respect to health indicators. Together, these results indicate that presumably beneficial and unfavorable microbiota genera relate to eating behavior and weight status, and that dietary fiber intake and SCFA metabolism may modify these relationships.

Bacterial genera

Due to the lack of associations with alpha diversity, except for subjective hunger, it remains difficult to draw strong conclusions on relations of eating behavior and microbial diversity, measured with Shannon index, based on the present BMI-defined overweight sample. The health-related microbiota group is comprised of bacterial genera that have been described as beneficial for the host in previous literature. For example, *Alistipes* and *Blautia* were found to produce SCFA [34, 35]. Similarily, *Gemmiger*, *Roseburia*, and *Ruminococcus* belong to the families of Ruminococcaceae or Lachnospiraceae, which share a common role as active plant degraders [36]. These positive metabolic effects on the host could eventually contribute to improved adiposity control, as e.g., higher *Blautia* was correlated to lower body fat [37], *Roseburia* was linked to lower blood glucose and *Ruminococcus* to higher weight loss in mice after vertical sleeve gastrectomy via regulation of nuclear

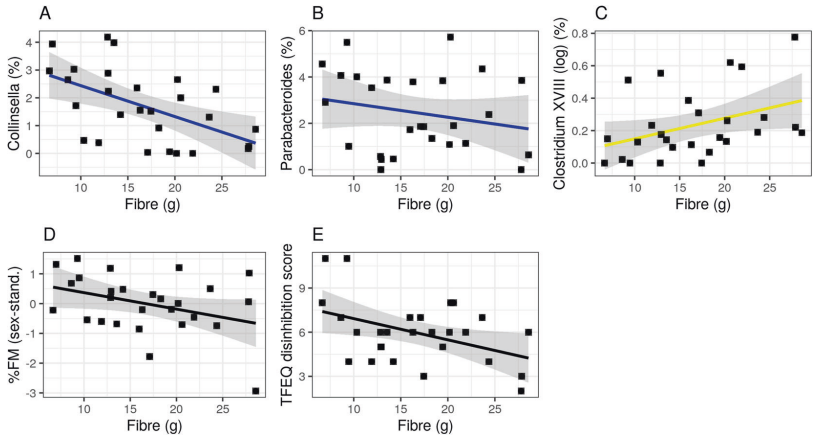

Fig. 3 Habitual dietary fiber intake is associated with bacterial genera, body fat mass and eating traits. Pearson's correlations shown for inversely health-related genera (blue) (**A**, **B**), health-related genera (yellow) (**C**), body fat mass (black) (**D**), and eating trait disinhibition (TFEQ) (black) (**E**) (Pearson's correlation all $0.75 < |r| > 0.58$, all p-FDR < 0.05; sample 1 $n = 27$).

receptor binding of bile acids [38]. A microbial transfer study from human to mice showed obesity-promoting effects of the species *C. ramosum*, which is part of *Clostridium XVIII* [39]. However, studies on the genera *Clostridium XVIII* and *Streptococcus* in relation to health are scarce. Clostridia are known to be key commensals for gut homeostasis [40], but classification of the genus *Clostridium* remains challenging due to the high heterogeneity of the listed species [41]. Also, there are currently 50 species identified in the genus *Streptococcus* alone, rendering different functionality in these genera likely. Yet, we found that *Clostridium XVIII* abundance related to higher dietary fiber intake, and *Streptococcus* abundance to lower blood pressure. Indeed, fiber intake related to healthy eating behavior and lower body fat mass in overweight young adults in the present analyses may point towards rather beneficial fiber-correlating *Clostridium XVIII* and *Streptococcus* genera species that underly those associations. Moreover, these results underline the potential impact of a fiber-rich diet for health indicators. Due to the exclusive occurrence of fiber in plants, fiber-rich diets are oftentimes attributed to plant-based (vegetarian or vegan) diets, and plant-based diets have been shown extensively to be beneficial for weight status, gut, and overall health [42, 43].

Considering the inversely health-related group of microbiota, some genera were described to include pathogens, e.g., in *Clostridium XIVb* the species *C. piliforme*, the causative agent of Tyzzer's disease [41] and *Parabacteroides* as an opportunistic pathogen in infectious diseases [44]. Of note, in the *Parabacteroides* genera, also beneficial species, e.g., *P. distasonis*, have been described [45]. The anaerobic *Collinsella* colonizes mucosal surfaces and has recently been reported to degrade potentially toxic food contaminants found in processed foods [46]. While this could be beneficial for the host, unhealthier eating behaviors (such as intake of processed food) and higher body weight could then likely be related to higher abundances of *Collinsella*. Likewise, studies showed that *Collinsella* linked to less dietary fiber intake, which is in line with our results in overweight adults, and higher weight loss in cross-sectional [47] and dietary intervention studies [48]. *Fusicatenibacter*, including the species *F. saccharivorans*, are strictly anaerobic sugar fermenters, again linking to unhealthier eating behavior and obesity [49]. The genus *Clostridum IV* however has rather been reported as beneficial SCFA producers, e.g., the species *Faecalibacterium prausnitzii* (*F. prausnitzii*), which play a noticeable role in intestinal homeostasis [50]. Yet again, those genera comprise many different species and it can also be speculated that some bacteria species or genera underlying the observed correlations could have likely been taxonomically misplaced [41]. Taken together, the negatively correlated microbiota genera seem to consist on the one hand of pathogens, indicative of a rather pro-inflammatory milieu in participants with higher weight status, which is well in line with our findings showing that higher *Parabacteroides* correlated with unhealthier eating traits and poorer weight loss maintenance in RYGB patients. On the other hand, those negatively correlated genera are comprised of those bacteria that metabolize processed food and sugars, again indicative of higher weight and unhealthy eating behavior. Future studies now need to integrate microbiota data at the species level and randomized interventional trials are required to eventually understand cause and effect of these eating behavior–microbiota–diet interrelations.

SCFA metabolism

We could not establish reliable links between serum and fecal concentrations of those metabolites. The overall weak relationship might be explained by rapid metabolization of SCFAs, as for example butyrate is rapidly absorbed by the gut mucosa and reaches blood circulation [51], therefore, fecal levels of butyrate may not directly relate to butyrate-producing bacteria abundance nor to serum levels of butyrate. In addition, biosamples of serum and feces were not collected in a time-locked way, therefore a time difference of hours to days might have blurred potential (inverse) correlations. Indeed, it has been shown, that fecal SCFA levels decrease throughout the day due to metabolization and that overnight-fast duration influenced these results [52].

Still, we found that higher fecal SCFA levels (i.e., acetate, butyrate, and propionate) linked to higher subjective hunger ratings and also to higher cognitive restraint (i.e., propionate), whereas lower acetate and butyrate in serum correlated with higher fat mass. Statistical path analyses proposed that higher *Parabacteroides* abundance link to higher hunger through higher fecal acetate. Bearing in mind that higher fecal SCFA levels may indicate less efficient absorption in the gut, leading to lower SCFA availability in serum [53], these findings are somewhat in line with studies showing reduced appetite and less weight gain after acetate intake [1, 54]. Note however, that we did not adjust

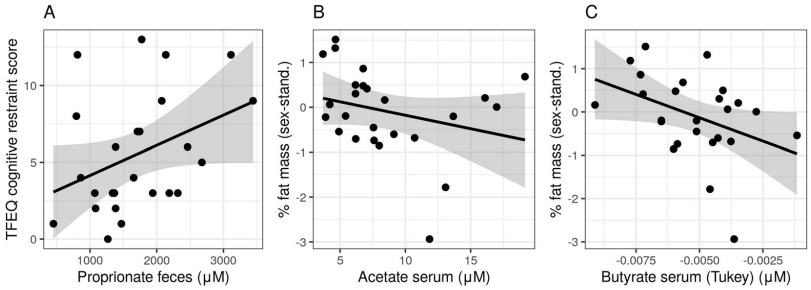

Fig. 4 SCFA levels in feces and serum are associated with eating traits and body fat mass in overweight adults (sample 1). Pearson's correlations shown for fecal SCFA levels and eating trait cognitive restraint (TFEQ) ($r = 0.50$, p-FDR = 0.014) (**A**) and serum SCFA levels with body fat mass for acetate (**B**) and butyrate (**C**) (all $r > -0.43$, all p-FDR < 0.04).

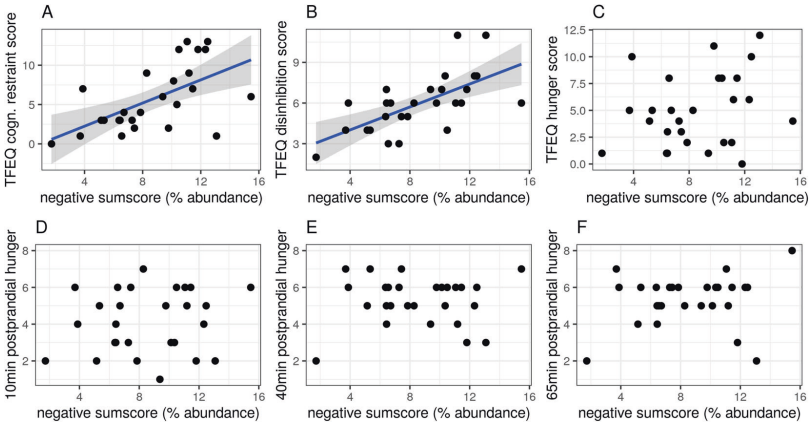

Fig. 5 Sumscore of inversely health-related genera is positively associated with eating traits (TFEQ). Pearson's correlations shown for microbial genera abundance sumscore for inversely health-related genera with respect to eating behavior outcomes from TFEQ and hunger ratings shown for **A**) cognitive restraint ($r = 0.59$, p-uncorr = 0.001) **B**) disinhibition ($r = 0.65$, p-uncorr < 0.001) **C**) hunger score **D**) 10 min-postprandial hunger **E**) 40 min-postprandial hunger and **F**) 65 min-postprandial hunger. Data from sample 1, all p-uncorrected.

mediation statistics for multiple testing, rendering false positives likely. In addition, it has been discussed that only a minimal fraction of the colon-derived SCFA directly reaches the brain. Instead, more downstream targets of SCFA signaling might be more important for gut–brain communication, such as SCFA-induced release of GLP-1 and PYY at the gut epithelium, modulation of liver metabolism or indirect signaling via the vagus nerve [1]. Future studies could help to further disentangle the different mechanisms at play by assessing further blood-, tissue- or imaging-based biomarkers of these pathways.

In an exploratory analysis, we found that body fat mass explains some of the variance in the observed relationships, especially in those with health-related commensals, and less with inversely health-related ones. Although BMI spanned within a very homogenous overweight status group (25–30 kg/m^2), body fat mass was quite variable (7–40%) in sample 1 and showed a significant influence of microbiome–behavior associations. This may hint to body fat as an important determinant of gut–behavior relations [55] that should receive further attention when designing dietary interventions targeting the gut microbiome.

Besides body fat, exploratory analyses showed no effects of sex/gender or common lifestyle factors on alpha diversity, yet these findings remain speculative because of small size and the cross-sectional nature of our analysis, therefore we cannot rule out that these or other factors such as medication might have confounded our analyses. Indeed, some studies reported on gut-modulating effects of nutrient supplementation such as in vitamin D [56] or vitamin B12 [57]. We recommend to document and report potential confounders in all microbiome analyses and encourage future data pooling and meta-analyses including our datasets (see open data).

Limitations

Firstly, all analyses are based on cross-sectional data, therefore no conclusions about causal relationships can be drawn. We performed exploratory analyses centered around core hypotheses with the aim to gain more specific testable hypotheses for upcoming intervention trials. In addition, both samples are limited by size, especially with regard to the larger number of variables of interest. Due to these constraints, more elaborate statistical analyses (such as structural equation modeling) could not be performed. A major strength of this study is the inclusion of two independent samples integrating next-generation sequencing and SCFA metabolomics with psychological markers in well-

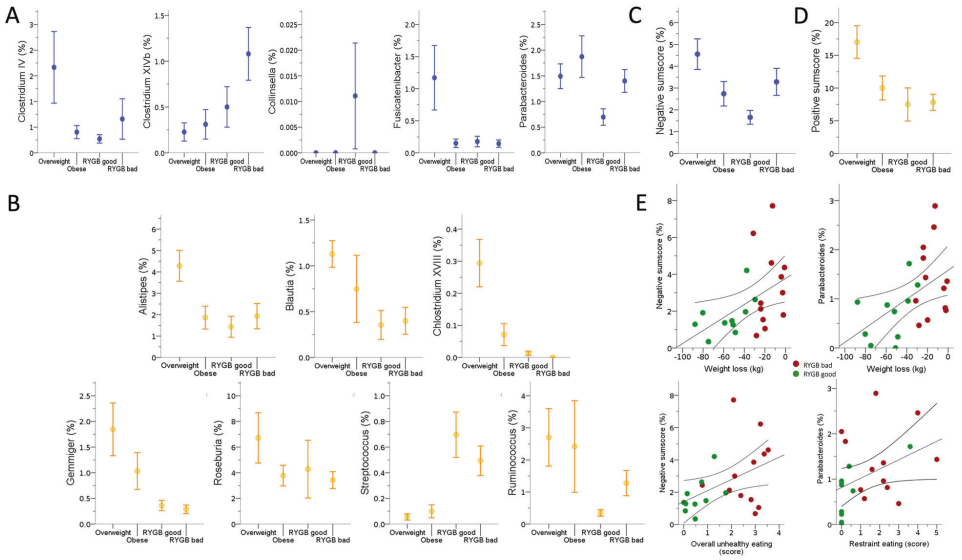

Fig. 6 Differences in relative bacterial genera abundance across groups of overweight, obese and post-RYGB adults in sample 2. For **A** inversely health-related (blue), **B** positively related genera (yellow), **C** negative (blue), and **D** positive sumscores of all related genera (yellow) detected in sample 1. **E** Correlation of negative genera sumscore and/or Parabacteroides abundance with eating behavior and/or weight loss after RYGB surgery (green: good responders; red: bad responders). RYGB, Roux-en-Y gastric bypass. Mean + SD.

Table 3. Potential confounders on gut microbiome associations.

Potential confounder on alpha diversity	Statistical test	*p*-value
Time of day	ANOVA: grouped by AM and PM time of stool collection	$p = 0.38$
Seasonality	ANOVA: grouped by season (divided into spring, summer, autumn, winter)	$p = 0.08$
Coffee intake	ANOVA: Three groups based on mean daily coffee intake (last 7 day FFQ) 0–0.3 ml/d 0.3–45 ml/d >45 ml/d	$p = 0.069$
Sex	t.test: segregated by sex	$p = 0.94$
Medication	Not tested due to limits in sample size (esp. sample 2)	–
% body fat mass	Partial correlations for all correlations shown in Figs. 2–4 adjusted for % body fat mass	see SI Table 5

Most of these additional exploratory analyses could be performed in sample 1 only, due to limited information in sample 2.

characterized adults at risk for future weight gain that yielded similar associations of eating behavior with gut microbiota at the genera level.

CONCLUSION

The combination of data from cross-sectional samples of overweight, obese, and post-bariatric surgery individuals showed multivariate associations between specific bacterial gut genera, particularly beneficial SCFA-producing genera and presumably unfavorable pathogens or sugar-/processed-food digesting bacteria, with anthropometrics, eating traits, and dietary fiber intake. While speculative concerning causality, our results propose key microbiota candidates for diet–gut–brain–behavior interactions in humans and may help to develop novel hypotheses how to prevent and treat unhealthy food craving through microbiotal modulation of the gut–brain axis. Longitudinal and interventional studies integrating metagenomic approaches and functional pathway analysis are needed to disentangle correlation from causality and to further characterize eating behavior-relevant microbiota genera at the species level.

DATA AVAILABILITY

All data generated during this study are included in this published article and its supplementary information files. Raw data cannot be shared due to data protection regulations.

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AUTHOR CONTRIBUTIONS
Conception and design of the study: EM, AVW, WF; collection of data in sample 1: EM, RT, CW, AVW: conception of study for sample 2: AH, WF; data management for sample 2: CF; RYGB surgery: AD; analysis of fecal microbiota: SBH; analysis of fecal and serum short-chain fatty acids: BE, URK; data analysis and interpretation: EM, AVW; manuscript drafting: EM, AVW. All authors read, revised, and approved the final manuscript.

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The authors declare no competing interests.

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For sample 1, Clinical Trials registration NCT03829189 and ethics proposal 228/18-ek, for sample 2 027/17-ek by the Ethics Committee of University Clinic Leipzig, Faculty of Medicine, Leipzig, Germany.

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Publication 3

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6	CLINICAL NUTRITION	12,594	6.402	0.018240
7	International Journal of Behavioral Nutrition and Physical Activity	9,914	6.037	0.020780
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10	FOOD CHEMISTRY	104,574	5.399	0.103870
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13	JOURNAL OF NUTRITIONAL BIOCHEMISTRY	10,544	4.490	0.012700
14	EUROPEAN JOURNAL OF NUTRITION	6,730	4.449	0.012210
15	JOURNAL OF NUTRITION	39,454	4.416	0.026850
16	Nutrients	19,332	4.171	0.047140
17	Journal of the Academy of Nutrition and Dietetics	4,815	4.141	0.013970
18	JOURNAL OF PARENTERAL AND ENTERAL NUTRITION	5,848	4.109	0.008210
19	Obesity	18,844	3.969	0.036270
20	NUTRITIONAL NEUROSCIENCE	1,778	3.950	0.002260

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Article

Less Animal-Based Food, Better Weight Status: Associations of the Restriction of Animal-Based Product Intake with Body-Mass-Index, Depressive Symptoms and Personality in the General Population

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Abstract: Restricting animal-based products from diet may exert beneficial effects on weight status; however, less is known about such a diet and emotional health. Moreover, personality traits, for example high neuroticism, may contribute to restrictive eating habits and potentially confound diet-health associations. We aim to systematically assess if restrictive dietary intake of animal-based products relates to lower weight and higher depressive symptoms, and if differences in personality traits play a significant role. Cross-sectional data from the baseline LIFE-Adult study were collected from 2011–2014 in Leipzig, Germany (n = 8943). Main outcomes of interest were dietary frequency of animal-derived products in the last year measured using a Food Frequency Questionnaire (FFQ), body-mass-index (BMI) (kg/m^2), and the Center of Epidemiological Studies Depression Scale (CES-D). Personality traits were assessed in a subsample of n = 7906 using the Five Factor Inventory (NEO-FFI). Higher restriction of animal-based product intake was associated with a lower BMI, but not with depression scores. Personality, i.e., lower extraversion, was related to lower frequency of animal product intake. Moreover, personality traits were significantly associated with depressive symptoms, i.e., higher neuroticism, lower extraversion, lower agreeableness, lower conscientiousness, and with higher BMI. These findings encourage future longitudinal studies to test the efficacy of restricting animal-based products as a preventive and therapeutic strategy for overweight and obesity.

Keywords: body weight; diet; plant-based; meat; depression; personality; population-based; cross-sectional

1. Introduction

Current debates assign animal product-restrictive eating patterns, such as vegetarian and vegan, either health benefits or risks [1]. For example, epidemiological studies such as the Adventist studies (n = 22,000–96,000) reported lower all-cause mortality rates and lower prevalence of cardiovascular diseases in participants with plant-based eating habits compared to those with omnivorous diets [2,3]. Other studies like the EPIC-Oxford study (n~64,000) [4] and the 45 and "Up Study" (n~267,000) [5],

however, showed no effect of a plant-based diet on mortality rate. An 18-year follow-up analysis of the EPIC-Oxford study showed, on the one hand, a decrease of ischaemic heart disease prevalence, and, on the other hand, an increased odds ratio for total stroke, in fish-eaters and vegetarians compared to meat-eaters [6]. Intervention studies in small to moderate sample sizes (n~100) indicated that medium-term vegan diets (12–74 weeks), compared to omnivorous diets, lead to weight loss and to a decrease in type 2 diabetes symptoms, even when caloric intake was comparably low between the diets [7–9].

While the exact mechanisms mediating these effects are far from fully understood, improved energy metabolism, reductions of systemic low-grade inflammation and changes in microbiome-gut-brain signaling might play a pivotal role [1,10–14].

Further, individuals showing restrictive eating patterns, i.e., excluding animal-derived food, may be more or less prone to develop mood disturbances compared to those with omnivorous eating styles: large epidemiological studies (n = 6422–90,380) showed higher depressive symptoms in vegetarians and vegans [15–17] and in those with orthorexic behaviour [18]. Yet other (smaller) cross-sectional (n = 620) and interventional (n = 39–291) studies proposed a positive effect of plant-based diets on well-being and subclinical depression scores [19–22]. Recently, it has been suggested that, not meat-restriction per se, but the number of excluded food groups predicts higher depressive scores [17].

In addition, weight changes relate to depressive symptoms [23], and obesity and depression might share genetic pathways and personality traits, in particular neuroticism [24]. For example, studies showed that higher neuroticism and lower conscientiousness correlate with a higher BMI and more depressive symptoms [25,26]. Moreover, differences in personality traits and in demographic factors such as age, sex and education have been linked to more or less restrictive lifestyle habits, including diet [27–29].

Taken together, these factors likely introduce confounding in studies assessing the relationship between diet, weight status and depressive symptoms separately. However, previous studies have not always accounted for these complex dependencies, rendering a definitive conclusion difficult as to whether animal product-restrictive eating habits convey health benefits or risks. We therefore aimed to systematically determine the interplay between animal-restrictive vs. omnivorous dietary habits (measured on a continuum as frequency of animal-based food intake), weight status, depressive symptoms and personality traits in a large population-based sample of adults in Germany.

We hypothesized that: (1) higher restriction of animal-based products is associated with lower BMI (kg/m^2), even when accounting for potential confounding factors; (2) higher restriction of animal-based products is associated with certain personality traits, measured using the Five-Factor Inventory (NEO-FFI); (3) higher restriction of animal-based products is associated with higher depressive symptoms scores (measured using CES-D), yet the association may attenuate when taking differences in demographics and personality traits into account.

2. Materials and Methods

All analyses and hypotheses have been preregistered in the Open Science Framework (OSF) at https://osf.io/4w69q. Participants were drawn from the population-based Leipzig Research Centre for Civilization Diseases (LIFE)-Adult cohort, which aims to explore causes and developments of common civilization diseases such as obesity, depression and dementia [28] (Figure 1). Briefly, n > 9500 adult participants ("Adult Baseline") were randomly selected based on sex and year of birth (age range 18–80 y, with a main proportion focus between 40–80 y), from the city registry of Leipzig, a major city with 550,000 inhabitants in the east of Germany. Additional volunteers (n > 900, randomly recruited from the city registry and from local databases, "Adult Baseline Plus") were included for periods of feasibility testing, piloting and finalization. Data collection was conducted from August 2011 to November 2014 at a single site in cooperation of the Faculty of Medicine, Leipzig University and the Max Planck Institute for Human Cognitive and Brain Sciences. All participants underwent anthropometric

measurements and answered extensive questionnaires regarding dietary habits, depressive mood and personality (see below for details).

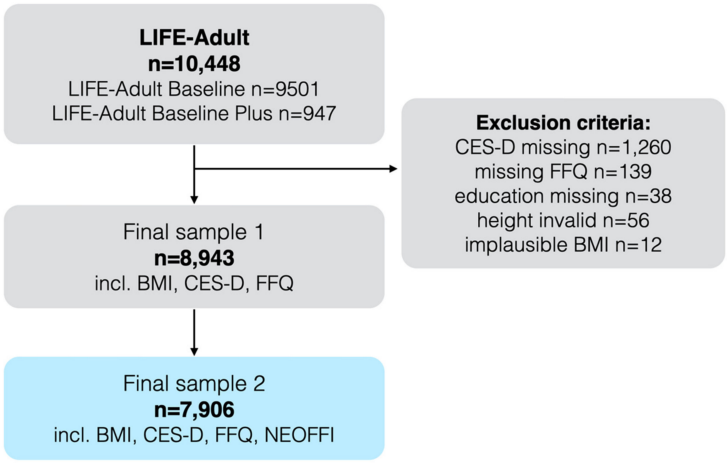


Figure 1. Flowchart of sample selection for sample 1 and sample 2. Abbreviations: BMI = Body-Mass-Index, CES-D = Center of Epidemiological Studies Depression Scale, FFQ = Food Frequency Questionnaire, NEOFFI=NEO Five-Factor-Inventory.

2.1. Inclusion Criteria

The initial dataset consisted of n = 10,083 participants. Subjects were included in the analysis based on standardized rules, if valid and complete measures of age, sex, education, BMI, CES-D and FFQ were available, resulting in a sample of n = 8943 (sample 1) and a subsample with additionally available personality trait measures of n = 7906 (sample 2, Figure 1). Note that results from sample 2 may slightly deviate from the previously reported pilot analyses in the OSF registration due to partially non-overlapping samples and an extension to a personality questionnaire that was widely available in the dataset.

2.2. Ethics

The institutional ethics board of the Medical Faculty of the University of Leipzig raised no concerns regarding the study protocol and all participants provided written informed consent. Code described in the manuscript will be made publicly and freely available without restriction at https://osf.io/m7hxk/?view_only=91863f44bae44371a1317072334df9fd.

2.3. Demographics

Education levels were computed according to Comparative Analysis of Social Mobility in Industrial Nations levels (CASMIN) [30] into three levels (low, middle, and high).

2.4. Anthropometry

Body weight was measured with scale SECA 701, height was measured with height rod SECA 220 (SECA GmbH & Co. KG, Hamburg, Germany). Body weight (kg) and body height (m) were used to calculate body-mass-index (BMI) (kg/m^2). For additional analyses WHO classification for obesity was used: underweight < 18.5 kg/m^2, normal-weight >= 18.5 and < 25 kg/m^2, overweight >= 25 and < 30 kg/m^2, obese >= 30 kg/m^2.

2.5. Personality

Personality traits were measured with the German version of the Big Five via Short Forms (16-Adjective Measure) [31]; subscales were computed for Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness by building summed scores according to the test's manual (higher scores indicate more pronounced traits, lower scores indicate less pronounced traits). In a subsample, personality traits were measured with the German version of the NEOFFI-30 [32,33].

2.6. Depressive Scores

Depressive scores (self-reported) were assessed by the Centre of Epidemiologic Studies-Depression (CES-D) scale [34]. Total CES-D score was calculated as a sum of responses to all 20 questions, with higher scores indicating more diverse and/or more frequent depressive symptoms.

2.7. Dietary Restriction Scores (DRS)

Food group items were taken from a questionnaire asking for self-reported food intake frequency over the last 12 months. A composite score for the restriction of animal-derived food items was calculated (Figure 2), including nine questions regarding the following food groups: meat, processed meat and cold cuts, fish, eggs, dairy (yoghurt and cream cheese), cheese, milk and butter (animal DRS). Answers ranged from multiple times daily (1 per item; 9 for summed score), daily/(almost) daily, multiple times a week, weekly, 2–3 times monthly, 1 or less a month to (almost) never (7 per item; 63 for summed score). The higher the score, the lower the frequency of consumption of animal-based products. Light products were recoded from 1–5 to 1–7, and either the normal or the light product was chosen for scoring depending on higher frequency; if both were equally frequent, the normal item was chosen (applicable for processed meat/cold cuts, dairy, cheese, butter and milk). Measures were ordinal, but for analysis purposes treated as linear, which is a common procedure for scoring lifestyle questionnaire data [35,36] and has been shown to perform robustly in parametric analyses [37]. Note that the questionnaire did not include an option such as "I prefer not to answer" or "I don't know". Missing values were replaced by the population mean in line with recommendation to use imputation for missing values in nutritional epidemiology [38]. Subjects with >20% of missing answers out of the 33 food items (excl. drink items) were excluded from the analysis (code and supplementary info available here (https://osf.io/m7hxk/?view_only=91863f44bae44371a1317072334df9fd).

To further investigate the difference between leaving out primary (meat, bone, and marrow, representing meat-restrictive diets) and/or secondary (stemming from animal labor, e.g., milk, representing vegetarian diets) animal products from the diet, we further tested whether potential associations were specific to either food groups by computing two additional scores: (a) primary DRS and (b) secondary DRS (Table S1).

An additional score represents the number of restricted food items (adapted from [17] by counting all *(almost) never* of 33 items in the FFQ (excluding drinks and light products) (score min. 0 to max. 33) within the last 12 months (5.1 ± 2.9 items (mean ± SD), range 0–19) (overall DRS).

All computed scores were normally distributed (skewness < 1.0, kurtosis <= 2.0) (Figure S1). Moderate positive correlations were observed between meat and cold cuts ($\rho = 0.46$), processed meat and meat ($\rho = 0.26$), processed meat and cold cuts ($\rho = 0.22$), dairy and cheese ($\rho = 0.42$), and dairy and milk ($\rho = 0.28$) consumption (Figure S2). A correlation matrix of all key variables of interest, including restrictive dietary patterns, BMI, depressive symptoms and personality traits is available (Figure S3).

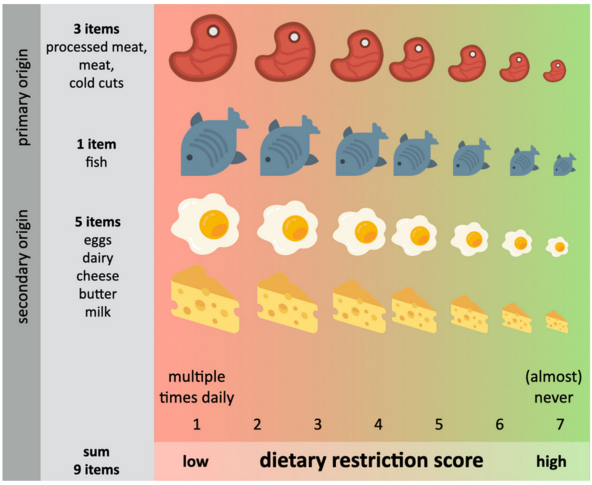


Figure 2. Concept of dietary restriction score (DRS) based on the frequency of consumption of animal-based products over the last 12 months based on nine items from the FFQ. Copyright icons: all icons by Smashicons.

2.8. Statistical Models

The main analysis included linear regression models to examine the association of animal DRS and BMI (model 1), depressive symptoms (model 3) and personality traits in a multivariate analysis of covariance (MANCOVA) (model 2). More specifically, model 1 tested whether animal DRS predicted BMI, adjusting for age, sex and education. Model 2 tested whether animal DRS (factor) was associated with the different personality traits (five subscales of the NEO-FFI as dependent variables), accounting for age, sex and education (covariates). Model 3 tested whether animal DRS predicted CES-D when accounting for age, sex and education; and, additionally, accounted for personality factors and BMI. All variables were normally distributed (skewness < |1.06|, kurtosis < |2.08|), personality traits (skewness < |1.05|, kurtosis < |3.2|), except for CES-D (skewness 1.4, kurtosis = 3.3), which was therefore log-transformed (log 10(CES-D+1). Analyses were computed in R version 3.6.1 using lm, lm.beta and ggplot2 for visualization. Statistical significance was set at alpha = 0.05/3 = 0.015 in the main analyses to adjust for multiple testing with the Bonferroni method and at $p < 0.05$ in all additional analyses.

3. Results

We included 8943 subjects for analyses regarding diet, BMI and depressive symptoms (see Table 1 for demographics), and 7906 participants in sample 2 for the subsample analysis additionally investigating personality traits (see Table 2). Due to the focus on the age range between 40–80 years in the selection of participants drawn from the city registry [28], the studied sample was on average middle-aged (mean age 57 y) and showed a skewed adult age distribution to the right. In addition, the study included slightly more women than men (4609F, 4334M) and a very wide BMI range (16–57 kg/m^2, on average 27.3 kg/m^2). About 2% of the sample (n = 237) reported to have adopted an exclusively vegetarian diet at least once throughout their life, and about 5% (n = 547) a mainly vegetarian diet.

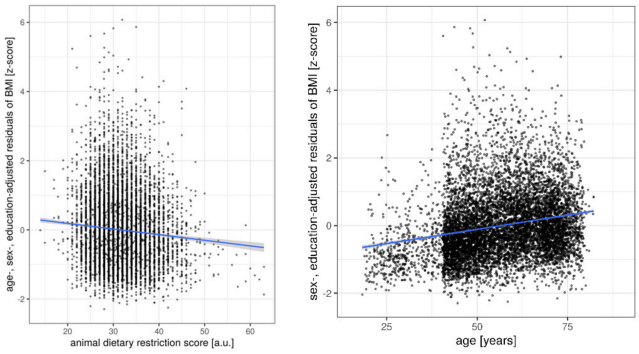
Table 1. Demographic characteristics for sample 1 and sample 2.

		Age (Years)	Sex	Education (CASMIN Levels)	Animal DRS (9–63)	BMI (kg/m^2)	CES-D (0–60)
Sample 1 (n = 8943)	**mean**	56.6 (18–82)	8943 (4609F)	2.28 (1–3)	31.53 (14–63)	27.25 (16.2–57.3)	10.69 (0–53)
	SD	12.5	-	0.6	5.1	4.9	6.9
Sample 2 (n = 7906)	**mean**	55.7 (18–82)	7906 (4010F)	2.31 (1–3)	31.55 (14–63)	27.16 (16.2–57.3)	10.57 (0–53)
	SD	12.4	-	0.6	5.1	4.7	6.9

Table 2. Personality traits according to the five factor personality questionnaire NEO-FFI (16 items) for sample 2 (n = 7906).

		Neuroticism	Extraversion	Openness	Agreeable-Ness	Conscientious-Ness
Sample 2 (n = 7906)	**mean**	13.2 (4–28)	10.9 (3–21)	16.3 (4–21)	11.7 (2–14)	23.6 (4–28)
	SD	4.4	3.7	2.7	2.0	3.2

Linear regression models detected that lower animal DRS, i.e., higher frequency of animal-based products consumption, related to higher BMI in sample 1 (n = 8943; β = −0.07, p < 0.001, Bonferroni-corrected), corrected for confounders (age, sex, education). Higher age, being male and lower education were also significantly associated with higher BMI, with the four factors together explaining about 6% of the variance in BMI (overall model adj. R^2 = 0.06, p < 0.001, Bonferroni-corrected) (Figure 3A, Table 3). Here, age showed the steepest slope (n = 8943; β = 0.08, p < 0.001; Figure 3B). Similar results emerged when restricting the analysis to the smaller sample 2 (data not shown). When additionally correcting for personality traits the association between BMI and animal DRS remains significant (n = 7906; β = −0.07, p < 0.001, Bonferroni-corrected), further certain personality traits show significant associations with BMI (neuroticism: β = −0.05, p < 0.001; openness: β = −0.05, p < 0.02; agreeableness: β = 0.13, p < 0.001; conscientiousness: β = −0.2, p < 0.001; all n = 7906) (Table 3).



(**A**) (**B**)

Figure 3. Association between body-mass-index (BMI) and demographic and lifestyle factors (**A**) animal DRS (**B**) age, residuals plotted according to regression model 1 (sample 1 n = 8943). Line gives regression fit. Point size = 1. Abbreviations: a.u. = arbitrary units.

Table 3. Multiple regression analyses predicting BMI as function of age, sex, education and frequency of animal-based products (n = 8943).

	Adj. R^2	B	C.I.	Beta	p
BMI (model 1)					
Model	0.06				<0.001
sex		−0.59	[−0.79 −0.40]	−0.06	**<0.001**
education		−0.67	[−0.83 −0.50]	−0.08	**<0.001**
age		0.08	[0.07 0.09]	0.21	**<0.001**
animal DRS		−0.07	[−0.09 −0.05]	−0.06	**<0.001**
BMI (model 1)—sample 2 (df = 7896), corrected for personality					
Model	0.08				<0.001
sex		−0.55	[−0.78 −0.33]	−0.06	**<0.001**
education		−0.65	[−0.83 −0.47]	−0.08	**<0.001**
age		0.09	[0.09 0.10]	0.24	**<0.001**
animal DRS		−0.07	[−0.09 −0.05]	−0.07	**<0.001**
neuroticism		−0.05	[−0.08 −0.03]	−0.05	**0.001**
extraversion		0.01	[−0.02 0.04]	0.01	0.42
openness		−0.05	[−0.10 −0.01]	−0.03	**0.01**
agreeableness		0.13	[0.07 0.19]	0.05	**<0.001**
conscientiousness		−0.20	[−0.23 −0.16]	−0.13	**<0.001**

B/beta represent unstandardized/standardized regression coefficients. Abbreviations: BMI = body-mass-index, DRS = dietary restriction score. Significant associations (p-values < 0.05) are indicated in bold.

Further, in sample 2 we found a significant association between frequency of animal-based products and personality traits, when correcting for age, sex and education (n = 7906; MANCOVA, $F_{(5,7897)} = 2.8$, $p < 0.02$): higher restriction of animal products was negatively associated with extraversion ($F_{(1,7897)} = 9.8$, $p = 0.002$) (Figure 4, Table 4). Although non-significant, animal DRS was positively associated with neuroticism ($F_{(1,7897)} = 3.5$, $p = 0.06$) and negatively with openness ($F_{(1,7897)} = 3.4$, $p = 0.07$). Likewise, sex was significantly associated with all five personality traits; and age and education with four of them (all except for agreeableness) (Table 4).

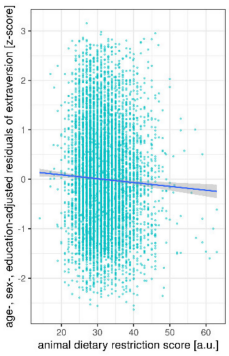


Figure 4. Association between animal DRS and extraversion, residuals plotted according to regression model 2 (sample 1 n = 8943). Line gives regression fit. Point size = 1. Abbreviations: a.u. = arbitrary units.

Table 4. Multivariate analysis of covariance (MANCOVA) analysis of animal DRS, age, sex, education on personality (n = 7906).

	Pillai's Trace	F	df	num df	den df	p
NEOFFI (model 2) (all factors, corrected for age, sex, education)						
sex	0.17	322.2	1	5	7897	**<0.001**
education	0.04	66.9	1	5	7897	**<0.001**
age	0.04	69.3	1	5	7897	**<0.001**
animal DRS	0.002	2.8	1	5	7897	**0.016**
NEOFFI Neuroticism						
sex		327.6	1	5	7897	**<0.001**
education		113.5	1	5	7897	**<0.001**
age		28.5	1	5	7897	**<0.001**
animal DRS		3.5	1	5	7897	0.06
NEOFFI Extraversion						
sex		15.9	1	5	7897	**<0.001**
education		71.1	1	5	7897	**<0.001**
age		152.7	1	5	7897	**<0.001**
animal DRS		9.8	1	5	7897	**0.002**
NEOFFI Openness						
sex		7.3	1	5	7897	**0.007**
education		208.4	1	5	7897	**<0.001**
age		4.6	1	5	7897	**0.03**
animal DRS		3.4	1	5	7897	0.07
NEOFFI Agreeableness						
sex		953.5	1	5	7897	**<0.001**
education		1.0	1	5	7897	0.33
age		0.7	1	5	7897	0.39
animal DRS		0.03	1	5	7897	0.87
NEOFFI Conscientiousness						
sex		137.4	1	5	7897	**<0.001**
education		10.7	1	5	7897	**0.001**
age		148.4	1	5	7897	**<0.001**
animal DRS		0.0006	1	5	7897	0.98

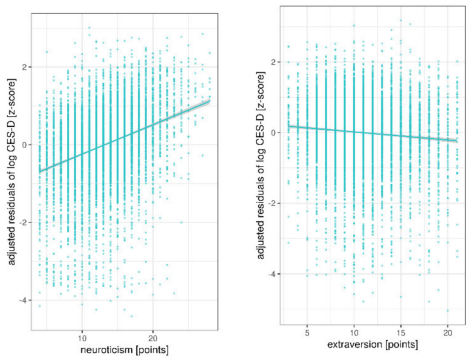
Abbreviations: DRS = dietary restriction score. Significant associations (p-values < 0.05) are indicated in bold.

Lastly, frequency of animal-based products did not predict variance in depressive symptoms in sample 1 (n = 8943, β = 0.001, p = 0.12), according to a linear regression model (model 3) that corrected for age, sex, and education (overall model: R^2 = 0.04, $p < 0.001$, Bonferroni-corrected) (Table 5). This was also the case for sample 2 (n = 7906, animal DRS: β = 0.001, p = 0.10; overall model; R^2 = 0.04; $p < 0.001$), also when additionally correcting for personality traits and BMI (n = 7906, animal DRS: β = 0.013, p = 0.2; overall model; R^2 = 0.21; $p < 0.001$) (Table 5). Instead, higher neuroticism (β = 0.4, $p < 0.001$), lower extraversion (β = −0.08, $p < 0.001$), lower openness (β = −0.07, $p < 0.001$), lower conscientiousness (β = −0.08, $p < 0.001$) and higher BMI (β = 0.06, $p < 0.001$) correlated with depressive symptoms (overall model explaining 21% of variance on depressive symptoms score) (Figure 5, Table 5).

Table 5. Multiple regression analyses predicting CES-D as a function of age, sex, education animal DRS (sample 1, n = 8493) and additionally personality traits (sample 2, n = 7906) and BMI.

	Adj. R^2	B	C.I.	Beta	p
CES-D (model 3)—sample 1 (df = 8938)					
Model	0.04				<0.001
sex		0.04	[0.029 0.051]	0.071	**<0.001**
education		−0.09	[−0.10 −0.08]	−0.184	**<0.001**
age		0.001	[0.0007 0.0016]	0.050	**<0.001**
animal DRS		0.001	[−0.0002 0.0020]	0.016	0.12
CES-D (model 3)—sample 2 (df = 7901)					
Model	0.04				
sex		0.04	[0.0273 0.0523]	0.069	**<0.001**
education		−0.09	[−0.1001 −0.0786]	−0.180	**<0.001**
age		0.001	[0.0006 0.0016]	0.049	**<0.001**
animal DRS		0.001	[−0.0002 0.0022]	0.018	0.10
CES-D (model 3)—sample 2 (df = 7896), corrected for personality					
Model	0.21				
sex		0.011	[−0.001 0.024]	0.02	0.08
education		−0.06	[−0.07 −0.05]	−0.12	**<0.001**
age		0.0006	[0.0001 0.0011]	0.03	**0.015**
animal DRS		0.0005	[−0.0006 0.0015]	0.009	0.40
neuroticism		0.024	[0.022 0.025]	0.36	**<0.001**
extraversion		−0.006	[−0.008 −0.005]	−0.08	**<0.001**
openness		−0.007	[−0.010 −0.005]	−0.07	**<0.001**
agreeableness		−0.0004	[−0.004 0.003]	−0.003	0.80
conscientiousness		−0.008	[−0.009 −0.006]	−0.08	**<0.001**
CES-D (model 3)—sample 2 (df = 7895), corrected for personality and BMI					
Model	0.21				<0.001
sex		0.013	[0.0008 0.026]	0.02	**0.04**
education		−0.06	[−0.082 −0.039]	−0.11	**<0.001**
age		0.0002	[−0.066 −0.046]	0.01	0.32
animal DRS		0.001	[−0.004 0.002]	0.013	0.20
neuroticism		0.024	[0.022 0.025]	0.36	**<0.001**
extraversion		−0.006	[−0.008 −0.005]	−0.08	**<0.001**
openness		−0.007	[−0.010 −0.005]	−0.07	**0.14**
agreeableness		−0.0009	[−0.004 0.003]	−0.006	0.60
conscientiousness		−0.007	[−0.009 −0.005]	−0.08	**<0.001**
BMI		0.004	[0.002 0.005]	0.06	**<0.001**

B/beta represent unstandardized/standardized regression coefficients. Abbreviations: BMI = body-mass-index, CES-D = depressive symptoms scale; DRS = dietary restriction score. Significant associations (p-values < 0.05) are indicated in bold.



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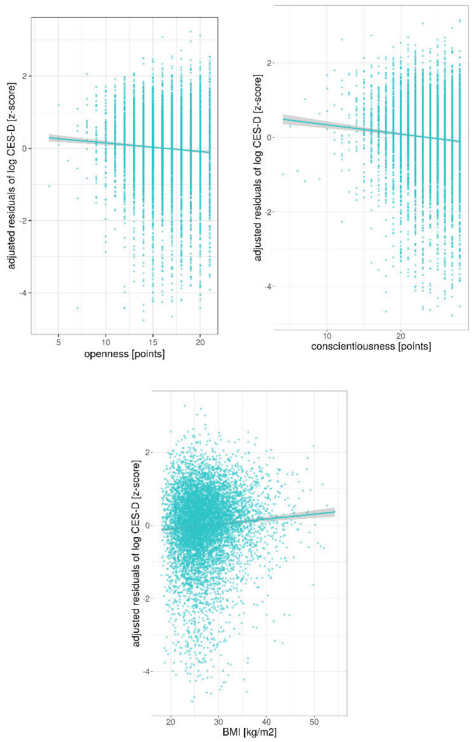

Figure 5. Significant association between personality traits and depressive symptoms in sample 2 (n = 7906) corrected for age, sex, education, animal DRS and the respective four other subscales of personality for neuroticism, extraversion, agreeableness, conscientiousness and BMI. Lines give regression fit. Position size = 2 (for personality) and 1 (BMI).

To confirm whether results were not driven by extreme cases with pathological underweight, we excluded underweight individuals (BMI <= 18.5 kg/m^2) from the analysis (n = 51, 17.8 ± 0.6 kg/m^2 (mean ± SD), range 16–18.5). This did not change the results from the main analyses (data not shown).

Ancillary Analyses

Restricting primary animal source products (i.e., (processed) meat, cold cuts) was significantly associated with a lower BMI (n = 8943; β = −0.25, p < 0.001, Figure 6), but not restricting intake of secondary animal products (cheese, milk, eggs) (n = 8943, β = −0.02, p = 0.16) (Table 6). Note the somewhat stronger association of primary animal-based products with BMI compared to the "comprehensive" animal-product DRS score, resulting in a more negative β coefficient.

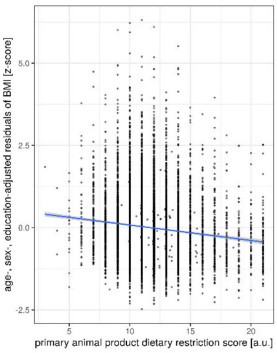

Figure 6. Restrictive animal-based product intake associated with lower BMI. Lines give regression fit. Position size = 1. Abbreviations: a.u. = arbitrary units.

Table 6. Multiple regression analyses predicting BMI as a function of age, sex, education and restriction of different dietary items (sample 1, n = 8493).

	Adj. R2	B	C.I.	Beta	p
BMI (model 1)—primary animal DRS					
Model	0.07				<0.001
sex		−0.18	[−0.38 0.03]	−0.018	0.10
education		−0.61	[−0.76 −0.44]	−0.074	**<0.001**
age		0.09	[0.08 0.10]	0.225	**<0.001**
primary animal DRS		−0.25	[−0.29 −0.21]	−0.132	**<0.001**
BMI (model 1)—secondary animal DRS					
Model	0.06				<0.001
sex		−0.63	[−0.84 −0.43]	−0.065	**<0.001**
education		−0.65	[−0.82 −0.49]	−0.079	**<0.001**
age		0.08	[0.07 0.09]	0.209	**<0.001**
secondary animal DRS		−0.02	[−0.04 −0.01]	−0.015	0.16
BMI (model 1)—overall DRS					
Model	0.07				<0.001
sex		−0.50	[−0.69 −0.30]	−0.051	**<0.001**
education		−0.70	[−0.83 −0.49]	−0.080	**<0.001**
age		0.09	[0.08 0.10]	0.221	**<0.001**
overall DRS		−0.15	[−0.18 −0.11]	−0.091	**<0.001**

B/beta represent unstandardized/standardized regression coefficients Abbreviations: BMI = body-mass-index, DRS = dietary restriction score. Significant associations (p-values < 0.05) are indicated in bold.

Investigating differences in personality, higher primary animal DRS was significantly associated with lower neuroticism ($F_{(1,7897)} = 27.5$, $p < 0.001$), higher openness ($F_{(1,7897)} = 45.1$, $p < 0.001$), higher agreeableness ($F_{(1,7897)} = 262.5$, $p < 0.001$) and higher conscientiousness ($F_{(1,7897)} = 63.1$, $p < 0.001$). Higher secondary animal DRS was significantly associated with lower extraversion ($F_{(1,7897)} = 11.1$, $p < 0.001$), lower openness ($F_{(1,7897)} = 26.9$, $p < 0.001$), lower agreeableness ($F_{(1,7897)} = 106.7$, $p < 0.001$) and lower conscientiousness ($F_{(1,7897)} = 14.2$, $p < 0.001$) (all: n = 7906, MANCOVA, corrected for age, sex and education) (Figure S4).

In contrast to the comprehensive animal product DRS, the scores displaying restriction of either primary or secondary origin animal products were also associated with lower and higher depressive symptoms scores, respectively (n = 8943, primary animal-product DRS: $\beta = -0.003$, $p = 0.04$; secondary animal-product DRS: $\beta = 0.002$, $p = 0.02$; models adjusted for age, sex and education). These divergent

associations, however, failed to reach significance when additionally correcting for personality traits (n = 7906, all $|\beta| < 0.002$, all $p > 0.10$, adjusted for age, sex, education and personality) (Table 7).

Table 7. Multiple regression analyses predicting CES-D as a function of age, sex, education and primary and secondary dietary restriction score (sample 1 $n = 8943$, sample 2 $n = 7906$).

	Adj. R^2	B	C.I.	Beta	p
CES-D—sample 1 (df = 8938)					
Model	0.04				**<0.001**
sex		0.05	[0.031 0.058]	0.08	**<0.001**
education		−0.09	[−0.100 −0.078]	−0.18	**<0.001**
age		0.001	[0.0007 0.0017]	0.05	**<0.001**
primary DRS		−0.003	[−0.005 −0.00008]	−0.02	**0.04**
CES-D—sample 2 (df = 7896), corrected for personality					
Model	0.21				<0.001
sex		0.014	[0.0008 0.0270]	0.02	**0.04**
education		−0.06	[−0.068 −0.048]	−0.12	**<0.001**
age		0.0006	[0.0001 0.0011]	0.03	**0.01**
primary DRS		−0.002	[−0.004 −0.001]	−0.01	0.21
neuroticism		0.024	[0.022 0.025]	0.36	**<0.001**
extraversion		−0.006	[−0.008 −0.005]	−0.08	**<0.001**
openness		−0.007	[−0.010 −0.005]	−0.07	**<0.001**
agreeableness		−0.0003	[−0.004 0.003]	−0.002	0.84
conscientiousness		−0.007	[−0.009 −0.006]	−0.08	**<0.001**
CES-D—sample 1 (df = 8938)					
Model	0.04				**<0.001**
sex		0.04	[0.032 0.055]	0.08	**<0.001**
education		−0.09	[−0.10 −0.08]	−0.20	**<0.001**
age		0.001	[0.0007 0.0016]	0.05	**<0.001**
secondary DRS		0.002	[0.0003 0.003]	−0.03	**0.02**
CES-D—sample 2 (df = 7896), corrected for personality					
Model	0.21				<0.001
sex		0.013	[0.0010 0.0261]	0.02	**0.05**
education		−0.06	[−0.068 −0.048]	−0.12	**<0.001**
age		0.0006	[0.0001 0.0011]	0.03	**0.01**
secondary DRS		0.001	[−0.005 0.002]	0.01	0.20
neuroticism		0.024	[0.022 0.025]	0.36	**<0.001**
extraversion		−0.006	[−0.008 −0.005]	−0.08	**<0.001**
openness		−0.007	[−0.010 −0.005]	−0.07	**<0.001**
agreeableness		−0.0003	[−0.004 0.003]	−0.002	0.84
conscientiousness		−0.008	[−0.009 −0.006]	−0.08	**<0.001**

Abbreviations: CES-D = depressive symptoms score, DRS = dietary restriction score. Significant associations (p-values < 0.05) are indicated in bold.

Further, we found a strong positive correlation between the frequency of animal-based products (animal DRS) and the number of restricted food groups considering all 33 items (overall DRS) ($\rho(8941) = 0.52$, $p < 0.001$) (Figure 7A).

Considering the number of restrictive food items in general, we found that a higher score of total excluded food items related to lower BMI (sample 1: $\beta = -0.15$, $t = -8.8$, $p < 0.001$, $R^2 = 0.07$, corrected for age, sex and education) (Figure 7B, Table 6).

The number of restricted food items was significantly associated with lower agreeableness ($F_{(1,7897)} = 15.7$, $p < 0.001$) and higher conscientiousness ($F_{(1,7897)} = 53.9$, $p < 0.001$) ($n = 7906$, MANCOVA, $F_{(5,7897)} = 11.8$, $p = < 0.001$, for model comparison against null model, corrected for age, sex and education) (Table 8).

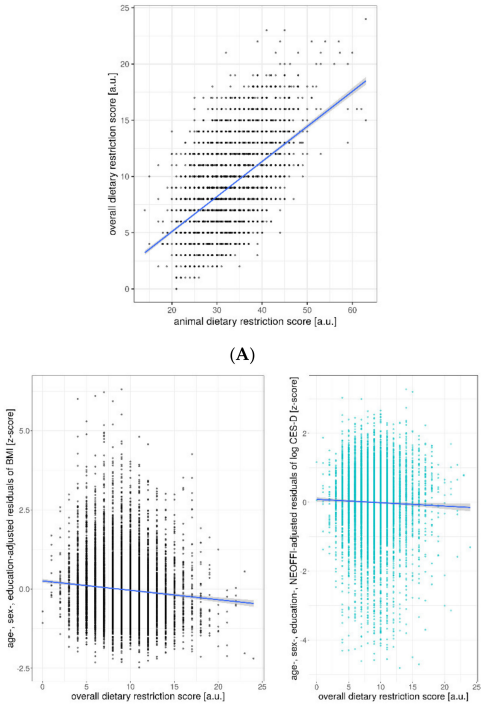

Figure 7. (**A**) Positive association between decreasing frequency of animal-based products and number of excluded food groups. Negative association between overall dietary restriction score with (**B**) BMI and (**C**) CES-D. Position size = 1. Abbreviations: a.u. = arbitrary units. Significant associations (p-values < 0.05) are indicated in bold.

Table 8. MANCOVA analysis of dietary restriction, age, sex, education on personality (n = 7906).

	Pillai's Trace	F	df	num df	den df	p
NEOFFI (all factors)—sample 2, corrected for age, sex, education						
sex	0.169	320.0	1	5	7897	<0.001
education	0.041	67.4	1	5	7897	<0.001
age	0.040	65.2	1	5	7897	<0.001
overall DRS	0.007	11.8	1	5	7897	<0.001
NEOFFI Neuroticism						
sex		342.0	1	5	7897	**<0.001**
education		114.5	1	5	7897	**<0.001**
age		28.9	1	5	7897	**<0.001**
overall DRS		0.6	1	5	7897	0.44
NEOFFI Extraversion						
sex		14.5	1	5	7897	**<0.001**
education		72.6	1	5	7897	**<0.001**
age		149.3	1	5	7897	**<0.001**
overall DRS		0.3	1	5	7897	0.6

Table 8. *Cont.*

	Pillai's Trace	F	df	num df	den df	p
NEOFFI Openness						
sex		6.1	1	5	7897	**0.01**
education		209.8	1	5	7897	**<0.001**
age		4.9	1	5	7897	**0.03**
overall DRS		1.6	1	5	7897	0.21
NEOFFI Agreeableness						
sex		937.3	1	5	7897	**<0.001**
education		0.9	1	5	7897	0.34
age		0.2	1	5	7897	0.7
overall DRS		15.7	1	5	7897	**<0.001**
NEOFFI Conscientiousness						
sex		122.4	1	5	7897	**<0.001**
education		10.7	1	5	7897	**0.001**
age		130.7	1	5	7897	**<0.001**
overall DRS		53.9	1	5	7897	**<0.001**

Abbreviations: DRS = dietary restriction score. Significant associations (p-values < 0.05) are indicated in bold.

Surprisingly, a higher number of restricted food items was weakly yet significantly associated with lower depressive symptoms scores ($\beta = -0.004$, $t = -4.1$, $p < 0.001$, $R^2 = 0.05$, corrected for age, sex and education) (similar results in sample 2 (data not shown)), also when additionally correcting for differences in personality traits ($\beta = -0.003$, $t = -2.7$, $p < 0.007$, $R^2 = 0.21$) (Figure 7C, Table 9).

Table 9. Multiple regression analyses predicting CES-D as a function of age, sex, education and dietary restriction score (sample 1 $n = 8943$, sample 2 $n = 7906$).

	Adj. R^2	B	C.I.	Beta	*p*
CES-D—sample 1 (df = 8938)					
Model	0.05				**<0.001**
sex		0.04	[0.032 0.055]	0.076	**<0.001**
education		−0.09	[−0.100 −0.080]	−0.185	**<0.001**
age		0.001	[0.0008 0.0017]	0.054	**<0.001**
overall DRS		−0.004	[−0.006 −0.002]	−0.043	**<0.001**
CES-D—sample 2 (df = 7901)					
Model	0.04				<0.001
sex		0.04	[0.031 0.056]	0.075	**<0.001**
education		−0.09	[−0.100 −0.080]	−0.180	**<0.001**
age		0.001	[0.0008 0.0017]	0.054	**<0.001**
overall DRS		−0.005	[−0.007 −0.002]	−0.048	**<0.001**
CES-D—sample 2 (df = 7896), corrected for personality					
Model	0.21				<0.001
sex		0.014	[0.0010 0.0261]	0.02	**0.04**
education		−0.06	[−0.068 −0.048]	−0.12	**<0.001**
age		0.0007	[0.0002 0.0011]	0.03	**0.007**
overall DRS		−0.003	[−0.004 −0.001]	−0.03	**0.007**
neuroticism		0.024	[0.022 0.025]	0.36	**<0.001**
extraversion		−0.006	[−0.008 −0.005]	−0.08	**<0.001**
openness		−0.007	[−0.010 −0.005]	−0.07	**<0.001**
agreeableness		−0.0005	[−0.004 0.003]	−0.004	0.76
conscientiousness		−0.007	[−0.009 −0.006]	−0.08	**<0.001**

B/beta represent unstandardized/standardized regression coefficients. Abbreviations: CES-D = depressive symptoms, DRS = dietary restriction score. Significant associations (p-values < 0.05) are indicated in bold.

4. Discussion

In this large cross-sectional analysis of ~9000 individuals from the general population, lower frequency of eating animal-based products was significantly associated with lower BMI, even when adjusting for confounding effects of age, sex and education. No significant associations emerged between animal-based products consumption and depressive symptom scores when taking personality into account. Frequency of animal-based product consumption was associated with personality traits, in particular with lower extraversion. Surprisingly, not diet but personality was significantly associated with depressive mood.

While the selection of our mid- to older age adult urban sample from Eastern Germany depended on the city registry of Leipzig, participants with a low social status and an unhealthy lifestyle were somewhat underrepresented compared to the general population [39]. However, the BMI range can be considered representative of a German population of this age.

4.1. Weight Status

Our finding that eating meat and dairy products less frequently relates to lower BMI is in line with some, but not all, epidemiological and moderate-term randomized interventional trials which point in this direction too [1,40,41]. In addition, results remained stable even after adjusting for education, which is a strong predictor of both obesity [42] and eating habits [43], and when taking inter-individual variance in personality traits into account [44]. Speculating on possible underlying mechanisms, animal-derived products in general are often denser in calories and in total and saturated fats compared to plant-based foods [45]. In addition, meat and dairy products are oftentimes consumed as processed food, e.g., processed meat, cold cuts, deep-fried meat/fish or high-processed snack products, further augmenting their caloric footprint. Thus, lower caloric intake might underlie the observed link between lower frequency of animal-based product consumption and lower BMI. Moreover, recent observations of changes in the gut microbiome due to diet raise the hypothesis that a different distribution of gut bacteria in plant-based dieters alters the ingestion rate of calories from food [46], thereby further limiting caloric intake (or bioavailability). However, while these causal pathways between lower frequency of animal-based product intake leading to lower or sustained body weight seem biologically plausible, the association between lower animal-based product intake and lower weight in our cohort might also be a result of lower body weight leading to less animal-based product intake or unknown shared factors that modulate both weight and diet. Future longitudinal observations and interventional trials are needed to further test the above-described hypothesis or its alternatives.

The positive association between restriction of meat products on weight status and the lack of a significant correlation for secondary animal products found in this study and previously by others [47–49] could possibly be explained by a higher proportion of highly processed meat items, leading to higher net energy intake and potentially to higher caloric intake [50]. Further, ongoing discussions on motivations for following certain diets support the view that restraint eating is not directly linked to vegetarian or vegan diets but more common in flexitarians who restrict meat intake with the goal of weight control, which in contrast is not the most common driver in plant-based dieters [51].

While, due to the cross-sectional design using self-reported FFQ data, estimates of absolute numbers of the strength of the association between diet and BMI are difficult, our findings may be relevant for public health. Considering that changing a conventional Western omnivorous dietary habit to a more plant-based diet, i.e., avoiding (processed) meat and cold cuts and limiting dairy, cheese and egg intake, would lead to an increase in animal DRS of 20 points, this would translate into ~1.2 kg/m^2 lower BMI. For someone with a frequent intake of primary and secondary animal-product intake (low animal DRS) this could mean, for example, reducing all animal-based products from multiple times a day to multiple times a week ("flexitarian diet") or excluding some animal items altogether ("vegan" or "vegetarian" diet). For a 175 cm tall human this would translate into 4 kg of body weight. If obese (e.g., 100 kg, i.e., BMI = 32.7 kg/m^2), this would mean a reduction of 4%

body weight; if overweight (e.g., 80 kg, BMI = 26.1 kg/m^2) this would mean a reduction of 5% body weight. As a reduction of 5–10% body weight has been shown to significantly reduce obesity-associated co-morbidities in overweight and obesity [52–58], restricting dietary intake of animal-based products may be one way to achieve this weight loss goal, and may help to reduce the societal burden of obesity-related diseases and environmental impact caused by high animal-product diets [40]. However, these calculations have to be interpreted with caution, as our findings rely on self-reported and cross-sectional data only, and we could not quantify dietary intake with regard to the consumed total amounts of food. Future longitudinal observations and interventional trials are needed.

4.2. Depressive Symptoms & Personality Traits

In contrast to previous large cross-sectional studies [16,17] and a prospective study in patients with inflammatory bowel disease [59], frequency of animal-derived product consumption did not explain variance in depressive symptoms scores in the current sample.

However, intervention studies showed that a plant-based vegan diet compared to a conventional omnivorous diet reduced anxiety and depression or emotional distress [19–22], proposing that restricting animal-based products per se may not affect mental health, but rather exert beneficial effects. Notably, we observed that different personality traits and BMI predicted depressive symptom score, which hints towards shared neurobiological mechanisms with obesity [23,25]. These shared mechanisms might help to explain previous inconsistent findings of a proposed link between restrictive diets and depression: certain personality traits may increase the probability of restricting certain food groups from diet, such as openness and conscientiousness [60]. Such a correlative link between personality and restrictive eating, although missing in the current data, would thus also apply to restricting animal-based products and may explain higher depressive symptoms in vegetarians or vegans [16]. Moreover, sociological studies show that animal-restricted dieters are often stereotyped with a multitude of biases: detrimental health effects, restrictive lifestyle, sentimentalism, extremism, lower perceived masculinity [61–63]. Aversion to plant-based dieters could lead to higher social exclusion and depressive symptoms as a result. However, more longitudinal studies tracking newly transformed dieters are needed to clarify if avoiding animal-derived products affects mental health.

Differences in our results compared to previous evidence on personality differences in vegetarians may be due to demographic and societal environmental factors. Personality trait differences in vegetarians were found in a cohort of college students [15], which might be different to our sample of the general population, in terms of beliefs, motivation of dietary habits, etc. Geographical or cultural settings may also influence differences in the results such as westernized (USA [15], Germany (this study)) versus mainly-vegetarian Indian cohorts [29], who showed higher conscientiousness. Lastly, the popularity and availability of plant-based dishes is a strong modulator of societal acceptance and demand for those kinds of diets. For instance, increasing the offer from one to two plant-based meals in canteens led to an increase of 40–80% of plant-based meal purchases, underlining the importance of availability as a strong driver [64]. Since the interest in plant-based diets has been changing dynamically in the last decade, researches should take period and location into account when comparing studies.

Strengths of our study comprise the large, well-characterized population based cohort enabling us to carefully control for important confounders such as education and personality. Moreover, recent studies and meta-analyses focused specifically on intake of red and processed meat and related health outcomes [65]. However the distinction of restricting diets to not consuming primary (vegetarian) and/or secondary animal-products (vegan) is oftentimes overlooked and therefore a strength of our study.

Our results further highlight a significant association of demographic variables with BMI, personality and depressive symptoms. This shows how individual factors such as age, sex and education are tightly linked to health (dis)advantages in our societies, and future studies on public health interventions should focus on those at particular risk, e.g., older males with lower education in

the case of BMI, and older females with lower education in the case of depressive symptoms. In parallel, the cross-sectional nature of our analysis does not allow us to imply causal relations, therefore future longitudinal and experimental interventional studies need to test to what extent modifiable factors, such as education, could causally reduce obesity and depression, and how dietary strategies such as reducing animal-based products might help to mediate these effects.

4.3. Limitations

Firstly, limitations of our study include that the results are based on a cross-sectional study design and therefore cannot explain underlying causalities.

Secondly, our analyses are based on self-reported dietary food record, which does not reflect actual food intake; however, test-retest reliability is generally of good quality [66]. The FFQ used in this study has been adopted from the frequently used German National Health Interview and Examination Survey 1998 [67], which has, however, not been validated, at least to our knowledge. Moreover, the FFQ used did not ask for quantity of food intake, which limits the interpretability of the observed effects (for further discussion on possible mechanisms see [1]) as important confounders such as total kcal intake could not be considered in this analysis. Yet, beside this possible inaccuracy of self-reported food intake, we propose that excluding certain food groups for a timeframe of twelve months is presumably a strong and reliable indicator of actual food intake and exclusion of certain food groups.

Thirdly, this study verifies depressive mood or depressive symptoms and not depression. The clinical interview remains the gold standard for identifying depression.

Fourthly, we did not account for ethnicity as these statistics were not available for this cohort. Based on historical data on immigration for this region, we estimate that the majority of the LIFE cohort were probably of Caucasian ethnicity and <1% were non-Caucasian.

Lastly, as frequently found in nutritional epidemiology, in our analysis socioeconomic status was accounted for by level of education, not income and occupational status [68]. This one-dimensional analysis might result in limited generalizability of the results. However, education can be viewed as a more long-term indicator of socioeconomic status compared to more dynamic monthly net income (as provided in this dataset).

5. Conclusions

Taken together, using a large cross-sectional analysis we observed that a lower frequency of animal-based products was related to lower BMI, while no link between animal-based products intake and depressive symptoms scores emerged. Thus, our findings may suggest that a lower frequency of animal-based products could be able to convey benefits on weights status, hinting to the capacity of plant-based diets as a potentially relevant target for the intervention of obesity and overweight, in particular by reducing the frequency (and probably the amount) of (especially primary source) animal-based products. Long-term interventional trials are needed to test this hypothesis and to clarify the underlying mechanisms.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/12/5/1492/s1, Figure S1: Frequency distribution of the dietary scores. (A) animal DRS (B) primary animal DRS (C) secondary animal DRS and D) overall DRS. All scores are normally distributed (skewness >0.5 and <1). E) Frequency distributions of 9 items used in animal DRS., Figure S2: Correlation plot of nine items included in animal DRS., Figure S3: Correlation plot of all measures of interest including dietary patterns, BMI, CES-D and personality traits. Figure S4: Associations frequency of animal-based products and personality traits (top row: primary DRS; bottom row: secondary DRS).Table S1: Summary of computed dietary restriction scores.

Author Contributions: Conceptualization, E.M., A.V., S.G.R.-H., A.V.W.; Methodology, E.M., A.V., A.V.W.; Formal Analysis, E.M.; Resources, A.V., S.G.R.-H.; Data Curation, E.M., C.E., S.R., A.V.W.; Writing—Original Draft Preparation, E.M., A.V.W.; Writing—Review & Editing, E.M., C.E., S.R., A.V., S.G.R.-H., A.V.W.; Visualization, E.M., A.V.W.; Supervision, A.V., A.V.W.; Project Administration, S.G.R.-H., A.V.W.; Funding Acquisition, A.V., A.V.W., S.G.R.-H. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: All authors declare no conflict of interest.

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Open and Sustainable Research

Beyond the topic of research, also the way in which research is conducted not only has an impact on future knowledge but also on the environment. For instance, it was shown that researchers in the European Union emit up to 300% additional emissions, i.e. 18 tCO_2eq / year, to their individual carbon footprint by professional activities in astronomy research (Jahnke et al. 2020). To counteract and improve ecological impact of research practises, next to advancing knowledge on climate-related topics, promoting and adopting open and sustainable research practices may be a suitable approach.

All herein presented and further related projects incorporate open research practises, including preregistration, released preprints, openly shared data and code upon publication and open access publishing.

Further, in a preprint we outlined how open science practises make research more sustainable in terms of ecological impact (Govaart, Hofmann, and Medawar 2021). Also, as a more institutionalized form of improving ecological impact of science, we founded the Max Planck Sustainability Network, which is a grassroots network aiming to make research within the Max Planck Society and beyond more sustainable by assessing and reducing ecological impact of research activities. I initiated a mission paper, which I am also the corresponding author of (Fardet et al. 2020).

Estimated ecological impact of the PhD work and compensation

Comprehensive and accurate estimations on CO_2eq linked to research remain very challenging. Yet, for my PhD it can be assumed that MR imaging had by far the highest energy consumption in terms of study methodology. Therefore, CO_2eq for each dataset including brain MRI was calculated based on manufacturer's information on energy consumption (kW), estimated hours of scan time per study (h), and CO_2 emission factor for Germany (kg/kWh), only considering active scan time for the study, excluding standby time of the MR scanner, sourcing and disposing of the machine and consumed liquid helium for cooling of the system.

Publication / Project	**Scanning hours and MR system**	**Estimated CO_2eq**
Medawar, Thieleking, et al. 2021, *PLOS ONE* Scanner upgrade study	121 participants x 1h x 2 scanners = 242h Siemens 3T Verio / 3T Skyra	2,95 t
Heinrichs et al. 2021, *Human Brain Mapping* ADIPOSITAS study	48 participants x 1h x 3 timepoints = 144h Siemens 3T Trio	3,40 t
Medawar, Thieleking, and Witte 2019, *OSF* GUT-BRAIN study	60 participants x 1.5h x 4 timepoints = 360h Siemens 3T Prisma	2,95 t
Total		**9,30 t** ~ 1,1 EU citizen's yearly emissions[2]

10 t CO_2eq were compensated to alleviate some of the ecological burden stemming from this particular research. I chose to support a project related to eating behaviour in Rwanda to provide efficient cookstoves that reduce wood consumption up to 80% or even more wood-intensive charcoal use (1kg charcoal requires 9kg wood). Further, monetary expenses for energy and air pollution are reduced.

[2] Based on per capita CO_2eq in 2019 published by the German Environmental Agency: https://www.umweltbundesamt.de/daten/klima/treibhausgas-emissionen-in-der-europaeischen-union#pro-kopf-emissionen (accessed on 6 Dec 2021)

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atmosfair betreibt seine Projekte nach den im Kyoto-Protokoll verankerten Regeln des Clean Development Mechanism (CDM) und zusätzlich dem von internationalen Umweltorganisationen etablierten „Gold Standard". Unabhängige, von den Vereinten Nationen zugelassene Organisationen (z.B. TÜV) kontrollieren die tatsächliche CO_2-Minderung der Projekte.

Gold Standard for the Global Goals

United Nations Framework Convention Climate Change

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Curriculum Vitae

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

Complete List of Publications

Akan, Ayça, **Evelyn Medawar**, A. Veronica Witte. Impacts of lifestyle interventions for obesity on gut microbiome: a systematic review (*in prep*). https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=281444

Beck, Kathrin, Johannes Bund, Tanguy Fardet, Nick Fischer, Wolfgang Goymann, Karl Hoffmann, Moritz Hütten, Knud Jahnke, Katharina John, Christoph Lenzen, Sophie Lohmann, **Evelyn Medawar**, Iris Möbius, Jan Renger, Jan Rybizki, Jakob Schweizer, Natalie Uomini, Andreas Voigt, and Marco Wietzoreck. 2021. Catalogue of Recommendations (CaRe) for Sustainability in the Max Planck Society / Katalog mit Empfehlungen für Nachhaltigkeit in der Max-Planck-Gesellschaft. https://doi.org/10.17617/1.mpsn.2021.01

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