

Objective measurement of physical activity in adults with ADHD and association with treatment outcome in a randomized controlled trial with a synbiotic intervention

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ABSTRACT

Background: ADHD is a neurodevelopmental disorder often persisting into adulthood. While Physical Activity (PA) is associated with improved ADHD symptoms in children, its effects in adults remain unclear. Emerging evidence suggests moderate PA enhances cognitive and behavioral functioning, though objective measurements are limited. Additionally, synbiotic interventions show potential in reducing ADHD symptoms, but possible synergies between PA and synbiotics are unexplored.

Objective: This study examines the relationship between objectively measured PA, ADHD diagnosis and severity in adults and assess whether PA influences synbiotic intervention effectiveness.

Methods: This is a secondary analysis of a subsample of the PROBIA trial (79 participants with ADHD, double-blind, randomized, controlled trial assessing a 10-week synbiotic intervention) and APPetite study (76 healthy controls). Forty participants in PROBIA received the synbiotic, 39 the placebo. PA was objectively measured via sensors tracking overall acceleration, Total Energy Expenditure (TEE), and moderate minutes of PA (MPA). Linear models, correlations, ANCOVAs, and regression analyses were used to examine associations between PA, ADHD symptoms, and treatment response to the synbiotic.

Results: PA did not significantly differ between the adult ADHD and control groups and was not correlated with ADHD symptom severity. PA did not predict symptom improvements, nor did it moderate the synbiotic effect.

Conclusions: PA seems similar in adults with ADHD and controls, and does not directly correlate with ADHD severity or specific symptoms. PA also did not moderate the effect of the synbiotic intervention. Further research needs to explore underlying mechanisms.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition characterized by inattention, hyperactivity, and impulsivity, affecting approximately 5% of children and persisting in 60-70% of adults (Berger et al., 2014; Rohde & Kiehl, 2010). In addition to pharmacological approaches, recent evidence points to

modifiable lifestyle factors as promising tools to reduce symptom severity: Both Physical Activity (PA) and exercise have been investigated in this regard (Dahlberg et al., 2025; Mehren et al., 2019), (where 'exercise' refers to structured physical activity delivered as an intervention, and 'PA' refers to everyday physical activity *without intervention*, including step counts, household work, general movement/activity assessed via wearable devices or self-report).

In addition to PA and exercise, nutritional interventions have also

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Glossary

ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS	ADHD Rating Scale
AEE	Activity Energy Expenditure
ARI-S:	Affective Reactivity Index Self-Report
BMI	Body Mass Index
BPD	Borderline Personality Disorder
CGI-S:	Clinical Global Impression-Severity
DIVA	Diagnostic Interview for ADHD in Adults
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
g	acceleration due to gravity (1 g = 9.81 m/s ²)

MDD	Major Depressive Disorder
MET	Metabolic Equivalent of Task
MINI	Mini International Neuropsychiatric Interview
MPA	Moderate Physical Activity
PSS	Perceived Stress Scale
RMR	Resting Metabolic Rate
sVCAM-1	soluble Vascular Cell Adhesion Molecule-1
TEE	Total Energy Expenditure (kcal/d)
Treatment	Synbiotic2000Forte400
UPPS-P:	Premeditation, Perseverance, Sensation Seeking and Positive Urgency
WHO	World Health Organization

shown beneficial effects: For instance, recent reports on synbiotics have shown beneficial effects for a range of symptoms (Arteaga-Henríquez et al., 2024; Skott et al., 2020). Interestingly, some evidence in healthy participants suggests that the effects of synbiotics may be enhanced in physically active individuals (Quero et al., 2021). As regular PA has been associated with greater gut microbiome diversity and a more favorable intestinal microenvironment (Yokoyama et al., 2021), PA may thus amplify the effects of a synbiotic supplementation (Hughes & Holscher, 2021; Yokoyama et al., 2021). In other words: higher physical activity may improve the outcome of symbiotic interventions and physical activity may thus be an important factor when considering treatment effects for synbiotics. This rising awareness of the interplay between nutrition and PA highlights the need to consider moderating associations between the two. However, to the best of our knowledge, this association has not yet been investigated in ADHD. Accordingly, we aimed to test whether physical activity moderates the effects of synbiotic supplementation in a randomized controlled trial of adults with ADHD with a focus on reduction of disease severity (i.e., inattention, hyperactivity, impulsivity) as the main outcome and secondary disease burden (i.e., perceived stress, depressive symptoms, BMI) as secondary outcomes. To understand these potential associations, it is first necessary to consider the literature on both topics separately and to examine evidence for possible moderation across existing studies.

1.1. PA and exercise in ADHD

As indicated above, although often used interchangeably, for the purpose of our manuscript, PA and exercise refer to different methodological concepts. We therefore first review evidence from exercise interventions, before turning to studies on everyday PA.

While often perceived as excessively active, children with ADHD may benefit from higher levels of exercise. In particular, an early meta-analysis (Cerrillo-Urbina et al., 2015) reported that structured aerobic exercise reduced core symptoms such as inattention, impulsivity, and hyperactivity. Some more recent meta-analytic findings also suggest that a moderate benefit can be observed particularly for the core symptom of inattention (Sun et al., 2022) and for executive functioning (Sun et al., 2022; Vysniauske et al., 2020), but not for hyperactivity (Sun et al., 2022). However, others reported non-significant reductions (Zang, 2019) or that the effect is no longer significant once publication bias is accounted for (i.e., for executive functioning see (Vysniauske et al., 2020)). Although the effects on the core ADHD symptoms may thus be smaller than initially assumed, structured exercise interventions have also been shown to significantly reduce comorbid anxiety and depression, thereby indirectly alleviating overall symptom burden (Zang, 2019).

Compared to children, research in adults with ADHD is limited, though growing (Dahlberg et al., 2025; Svedell et al., 2025; Yang et al., 2025). A recent systematic review and meta-analysis (Dahlberg et al.,

2025) has investigated the effect of single and multiple sessions of various exercise types in 13 studies for 312 adults with ADHD: they found a small, significant reduction in symptoms for the single session, while the chronic exercise interventions (i.e., multiple sessions) did not lead to significant symptom improvement. The subgroup analysis of 4 studies did however show that longer interventions seemed to show stronger reductions in ADHD symptoms (without further specification in symptom subtype). Earlier work which predominantly examined exercise effects in children and included only four studies in adults, provided preliminary evidence that structured exercise interventions may also be associated with beneficial outcomes (i.e., reduction in impulsivity, inattention, depression) in adults with ADHD (DenHeijer et al., 2016). Others have supported this notion by showing that acute exercise can enhance attention and concentration (Kallweit et al., 2021).

In contrast to exercise, PA in everyday life may represent a more natural and ecologically valid lifestyle factor, as opposed to a deliberate intervention: That is, where exercise can be defined as a planned, structured, repetitive, and purposive activity to improve or maintain one or more components of physical fitness (Caspersen et al., 1985), PA refers to any bodily movement produced by skeletal muscles that requires energy expenditure, such as walking, household chores, or commuting (World Health Organization, 2020). Literature provides evidence of a symptomatic shift in ADHD over time, with hyperactive behaviors in childhood often giving way to more inattentive symptoms in adulthood (Biederman et al., 2000; Cortese et al., 2012). Likewise, a shift in PA levels can be observed across development: While young children with ADHD are more likely to meet recommended PA guidelines (Bustamante et al., 2019), this initial advantage tends to decline or even reverse during adolescence (Cook et al., 2014; Quesada et al., 2018), though longitudinal evidence for this effect is missing. However, literature on PA measured with wearable technology is still scarce: To our knowledge, there are currently only about ten studies (Abramovitch et al., 2013; Berger et al., 2014; Björk et al., 2018; DenHeijer et al., 2016; Fritz & O'Connor, 2016; Gapin et al., 2015; Kallweit et al., 2021; Koch et al., 2022; Mehren et al., 2019; Ruf et al., 2023) that assess PA in adults with ADHD, with few of them assessing symptom severity (see Supplementary Table 1). In addition, important shortcomings such as the assessment of PA using questionnaires or e-diaries (Fritz & O'Connor, 2016) or small sample sizes (Gapin et al., 2015; Kallweit et al., 2021) hamper the reliability of current results. Evidence supporting the positive effects of exercise interventions is growing - for ADHD symptoms in adults (Dahlberg et al., 2025) and for cognitive and behavioural outcomes in adults and in children (DenHeijer et al., 2016). However more research on everyday PA-particularly for adults with ADHD-is needed. Studies using objective measurements of everyday PA (e.g., wearable technologies) could help advance our understanding whether there is a relationship between PA and ADHD symptomatology.

1.2. A synergistic effect of PA and synbiotics?

As mentioned above, beyond PA, nutrition is increasingly recognized as a key factor in managing general health and potentially, affecting ADHD symptoms. Synbiotics (pre- and probiotics) have shown several improvements in ADHD-related symptomatology, albeit no consistent pattern has yet emerged: For example, in the primary analysis of the here reported PROBIA study (Arteaga-Henríquez et al., 2020) synbiotic supplementation in adults with ADHD improved inattention and perceived stress levels, whereas the study by (Skott et al., 2020) found improved emotion regulation in adults with ADHD for goal-directed behaviour, particularly when a marker of inflammation (i.e., sVCAM-1) was elevated at baseline. The question regarding the working mechanisms for these observed effects is not fully elucidated yet. It has been suggested that synbiotics and comparable interventions influence symptomatology via the gut–brain axis and/or improved gut microbiome composition in terms of diversity and function, potentially also improving immune system function (Arteaga-Henríquez et al., 2024) others have suggested indirect effects due to secondary effects of nutrition such as metabolic changes and weight loss: Indeed, several studies have reported that pre- and probiotic supplementation can significantly reduce body weight, BMI, and waist circumference and meta-analyses have shown significant effects (Saadati et al., 2023). Adults with ADHD often show significantly elevated BMI compared to neurotypical controls (Björk et al., 2018); a shift in BMI following synbiotic supplementation could influence the interpretation of treatment-related effects. As BMI is an established marker of cardiometabolic health, and deviations from the normal BMI range have been associated with increased all-cause mortality (Di Angelantonio et al., 2016), changes in BMI following synbiotic supplementation may hold direct clinical relevance beyond core symptom improvement. Moreover, as BMI and adiposity are closely tied to gut microbiome composition (Le Chatelier et al., 2013; Ley, 2010), assessing change in BMI may therefore help identify treatment-related metabolic changes and account for a potential confounding factor within the gut–brain axis framework underlying this study.

An alternative possibility is that synbiotics indirectly promote increased PA, or that their effects are enhanced by synergistic activity. For instance, PA is also known to improve gut microbiota composition in terms of diversity and function (e.g., increased short chain fatty acid production capacity) (Fontana et al., 2023; Hawley et al., 2025; Kazeminasab et al., 2024; Varghese et al., 2024) which in turn has been linked to more favorable mental health outcomes (Shaikh et al., 2025) as well as a more beneficial intestinal microenvironment overall (Yokoyama et al., 2021). PA also has generally beneficial effects on general health outcomes like metabolism and BMI, potentially allowing an amplification of the above mentioned, synbiotic-associated effects. Partially in line with this hypothesis, one recent article reported *Lactobacillus* levels showing differential associations with BMI depending on individuals' PA levels (Wu et al., 2025), and a recent meta-analysis in non-alcoholic fatty liver disease found that a probiotic combined with exercise training resulted in improved lab results for liver enzymes, lipid profile, and insulin resistance compared to exercise alone (Kazeminasab et al., 2024). Converging evidence further suggests that PA and nutritional factors may interact in their effects on mental health outcomes, with high PA combined with high diet quality associated with greater reductions in depressive symptoms than either factor alone (Kim & Park, 2026).

In addition, a recent article showed that supplementation of synbiotics led to an improvement in objective PA measurements and sleep quality, perceived general health, stress, and anxiety levels in athletes (Quero et al., 2021). Therefore these associations have yet to be investigated in non-athlete populations, raising the possibility that PA levels influence the synbiotic-related improvements (Quero et al., 2021). Interestingly, pre- and probiotics have also been suggested to increase athletic performance (Hughes & Holscher, 2021) and synbiotics are

frequently used in athletes, where they show a favorable influence on stress factors such as sleep quality, gastrointestinal symptoms, and well-being indicators (Quero et al., 2021; Valle et al., 2021). Similarly, exercise and greater muscle mass appear to have an independent positive association with the gut microbiome and inversely, people with lower muscle mass tend to have a weakened intestinal microenvironment (Yokoyama et al., 2021). Together, these findings raise the question whether PA may be a relevant independent or a moderating predictor for treatment outcomes of synbiotics, but to our knowledge, evidence on this question is still lacking with regard to ADHD.

In summary, this study is an exploratory analysis of data obtained during the PROBIA trial, which aims to address critical gaps in the ADHD literature by investigating a) whether objectively measured PA is associated with ADHD diagnosis and symptom severity in adults, and b) whether PA moderates the effectiveness of a synbiotic intervention on symptom outcomes and c) whether synbiotic supplementation leads to a reduction in BMI in adults with ADHD. We hypothesize that PA levels are lower in adults with ADHD compared to controls and that higher levels of activity will be associated with reduced symptom severity. Furthermore, we propose that PA may enhance the beneficial effects of synbiotic treatment, reflecting a synergistic interaction between behavioral and nutritional interventions. Finally, given the elevated BMI observed in adults with ADHD and the established effects of synbiotics on body composition in the general population, we hypothesize that synbiotic supplementation may lead to a reduction in BMI in adults with ADHD.

2. Methods

The data used in this article has been obtained from the Probiotics for Impulsivity in Adults (PROBIA (Arteaga-Henríquez et al., 2020, 2024), and the APPetite studies (Ruf et al., 2021, 2023). Research procedures adhered to the relevant national and institutional Good Clinical Practice (GCP) guidelines on human experimentation, as well as to the Declaration of Helsinki of 1975, as reviewed in 2008. Ethical approval for participants with ADHD has been obtained in the PROBIA study from the 3 regional ethical committees (Budapest:44101-1/2018/EKU; Barcelona:311/2018; Frankfurt:269/18) and registered at the clinical trials registration platform *ClinicalTrials.gov* (NCT03495375, registered on 02/2018). The present study constitutes a secondary analysis of data from the PROBIA trial. The design, randomization, blinding procedures, intervention details, primary and secondary outcomes, and safety assessments of the original trial have been reported in detail elsewhere (Arteaga-Henríquez et al., 2020, 2024). The current manuscript focuses on analyses specific to objectively measured PA and treatment response.

Ethical approval for the healthy control group was obtained for the APPetite study at the local committee in Frankfurt (reference number: 192/18). Written informed consent was obtained prior to any study related procedures.

The PROBIA study was a prospective, multicenter, double-blind, randomized, placebo-controlled trial (allocation ratio 1:1) with initial data collection beginning in February 2019 and the study concluded in May 2021, after all required participants had been recruited. Conducted at three European clinical centers, this trial included adults with a confirmed current diagnosis of ADHD or borderline personality disorder and high levels of chronic irritability (Arteaga-Henríquez et al., 2020). For the purpose of this study only participants with ADHD were considered. The APPetite study was an observational study conducted in Frankfurt, Germany. Only full datasets available at the time of analysis (06/10/2023) of the APPetite study were considered for this paper. It used the APPetite-mobile-app (Ruf et al., 2021, pp. P1–P17) for ecological momentary assessment of microtemporal, within-person processes including dietary intake and objectively recorded PA in healthy controls and psychiatric patients. For this analysis, only the healthy control group is considered. For this secondary analysis only participants with available data for PA were considered.

2.1. Participants

A flow diagram of the participants in the clinical trial and the subset used in this study can be found in the supplementary material. In this study only participants with ADHD and healthy controls were considered. Inclusion criteria comprised a high level of chronic irritability (i.e., an Affective Reactivity Index Self-Report (ARI-S) (Stringaris et al., 2012) ≥ 5 plus a Clinical Global Impression-Severity (CGI-S) (Guy, 1976; Kadouri et al., 2007) total score ≥ 4 (i.e., moderately ill)). Age range was between 18 and 65 years. Participants were excluded from the study if they showed past and/or current psychotic symptoms, or if they had any major neurological, cardiovascular, endocrine, pulmonary, immunological and/or gastrointestinal disorder at screening. Participants on anti-inflammatory and/or psychiatric medications were included only if the type of agent and dosage had been stable for at least 30 days prior to study entry. Conversely, participants who had undergone immunosuppression or had taken antibiotics or probiotics within the 30 days prior to study entry were excluded. Participants of the control group were free of psychiatric disorder as confirmed with a MINI Psychiatric Interview (Sheehan et al., 1997; Sheehan et al., 1998; Van Vliet & De Beurs, 2007; “Deutsche Fassung des Mini-International Neuropsychiatric Interview” 1999). See Table 1 for demographics and Table 1.1 for the demographics of the intervention group.

2.2. Procedures

The methods of the PROBIA study are reported in detail elsewhere (Arteaga-Henríquez et al., 2020). In brief, the study investigated the effects of Synbiotic2000Forte 400, a synbiotic, compared to a placebo over a 10-week period in highly impulsive adults (aged 18-65) diagnosed with ADHD and/or borderline personality disorder (BPD). The ADHD diagnosis was confirmed by trained raters using the DIVA interview. Participants were randomly assigned to receive either the synbiotic or a placebo for 10 weeks, taken twice daily, with food or drinks. Placebo and Synbiotic looked similar and were provided in similar packaging. Randomization was performed by a research assistant who was not involved in the study, by the use of an independent randomization service. Random block sizes were applied to control the number of participants assigned to each group, stratified by site (for details, refer to (Arteaga-Henríquez et al., 2024)). Participants were blinded to the allocated group. The study was conducted with 180 adults, with at least 30% being female, with a high level of impulsivity. The primary outcome was measured by the reduction in irritability scores (ARI-S) and overall clinical improvement (CGI-I) at the end of the treatment period.

Table 1
Demographic and clinical characteristics.

Variable	Control (n = 76)	ADHD (n = 79)	p (statistics)
Age Mean (SD)	29.2 (8.5)	39.3 (10.9)	0.000 (W: 4581.500)
BMI Mean (SD)	23.9 (3.5)	27.2 (5.7)	0.000 (t: 4.362)
Male (n)	19	37	0.008 (chi square: 7.085)
Female (n)	57	42	
ADHD-Score Baseline Mean (SD)		33.2 (8.34)	
Subscore Inattention Baseline Mean (SD)		16.8 (4.54)	
Subscore Hyperactivity Baseline Mean (SD)		8.87 (3.46)	
Subscore Impulsivity Baseline Mean (SD)		7.43 (2.99)	
UPPS Score Baseline Mean (SD)		137.7 (14.7)	
Wake wear-time Mean (SD)	15.3 (1.86)	15.6 (2.6)	0.513 (t: 0.656)
MPA per week Mean (SD)	202.5 (190.4)	210.2 (217.7)	see RQ1

Table 1.1

Demographics by treatment group.

Variable	Synbiotic (n = 40)	Placebo (n = 39)	p (statistics)
Age Mean (SD)	39.12 (10.77)	39.51 (11.15)	0.876 (t:- 0.157)
BMI Mean (SD)	26.68 (5.50)	27.75 (5.95)	0.411 (t:- 0.826)
Male (n)	22	15	0.212 (chi ² : 1.556)
Female (n)	18	24	
ADHD-Score Baseline Mean (SD)	33.3 (7.92)	32.8 (8.65)	0.785 (t: 0.274)
Subscore Inattention Baseline Mean (SD)	16.9 (4.69)	16.5 (4.39)	0.707 (t: 0.378)
Subscore Hyperactivity Baseline Mean (SD)	8.95 (3.3)	8.56 (3.65)	0.619 (t: 0.500)
Subscore Impulsivity Baseline Mean (SD)	7.32 (2.85)	7.51 (3.01)	0.777 (t: -0.285)
UPPS Score Baseline Mean (SD)	141 (14.4)	135 (14.9)	0.095 (t: 1.693)
Wake wear-time Mean (SD)	15.6 (2.53)	15.5 (2.71)	0.908 (t: 0.115)
MPA per week Mean (SD)	214.2 (203)	205.8 (234.5)	0.868 (t: 0.167)

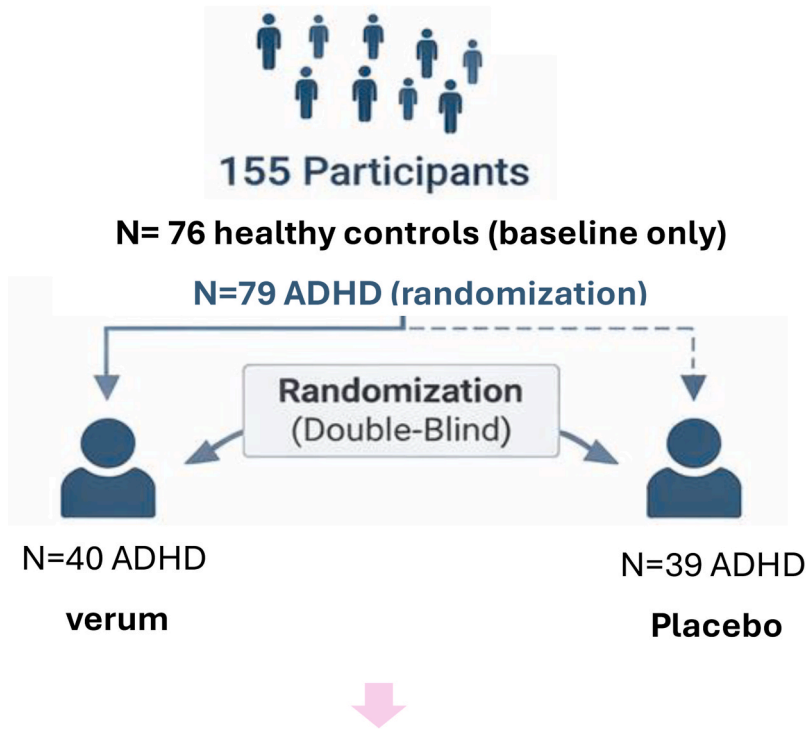
Secondary outcomes evaluated the synbiotic's effectiveness in managing emotional dysregulation, symptoms of impulsivity, compulsivity, inattention, functioning, and perceived stress. See Fig. 1. Additionally, changes in BMI, nutrient intake, and PA from baseline to week 10 were assessed. Participants underwent several study visits: The first visit, known as the Screening Visit (TS), involved confirmation of the diagnosis and initial assessments to establish eligibility. Following this, the Baseline visit (T0) occurred within a week of screening, during which baseline assessments were conducted and participants were introduced to the intervention. The Mid-Intervention visit (T1) took place 5 weeks after T0, where primary and secondary outcome measures were evaluated. The post-intervention visit (T2) was scheduled after 10 weeks to conduct a final assessment of the outcomes. Finally, a Follow-Up visit (T3) was held one week after the intervention to assess the safety and any residual effects of the treatment. PA data was collected using sensors during the baseline period (TS) and at T2, covering four days for each period to gather comprehensive PA data. Participants wore sensors on two weekdays and a weekend for 24 h each day.

The APPetite study includes two in-person sessions to collect various psychological and physiological parameters, along with a one-week ambulatory assessment of diet, impulsivity, affect, and PA using a mHealth app and activity sensors. A follow-up after three months involves a reassessment of dietary data. Additionally, an optional MRI scan is offered for structural brain imaging.

2.3. Measurements

For this secondary analysis, our main outcomes were general ADHD symptoms (ADHD Rating Scale (DuPaul et al., 2007) including subscales), and impulsivity (UPPS-P) (Kämpfe & Mitte, 2009; Whiteside & Lynam, 2001). Secondary outcomes were stress and depression which were measured with PSS (Perceived Stress Scale) (Cohen et al., 1983) and MDE (Major depressive episode, based on the criteria of the DSM-5, the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013)). For the intervention analysis, we examined synbiotic effects on activity levels, ADHD symptoms (ADHD-RS, UPPS-P), and BMI. PA was measured via an acceleration sensor (LightMove 3, movisens GmbH) worn on the non-dominant wrist, with a ± 8 g range and 64 Hz sampling frequency. Raw data was processed using the DataAnalyzer software (version 1.13.7), with incorporated biological parameters (height, weight, age, sex) to compute movement acceleration, energy expenditure and MET. Key variables

A



B STUDY DESIGN

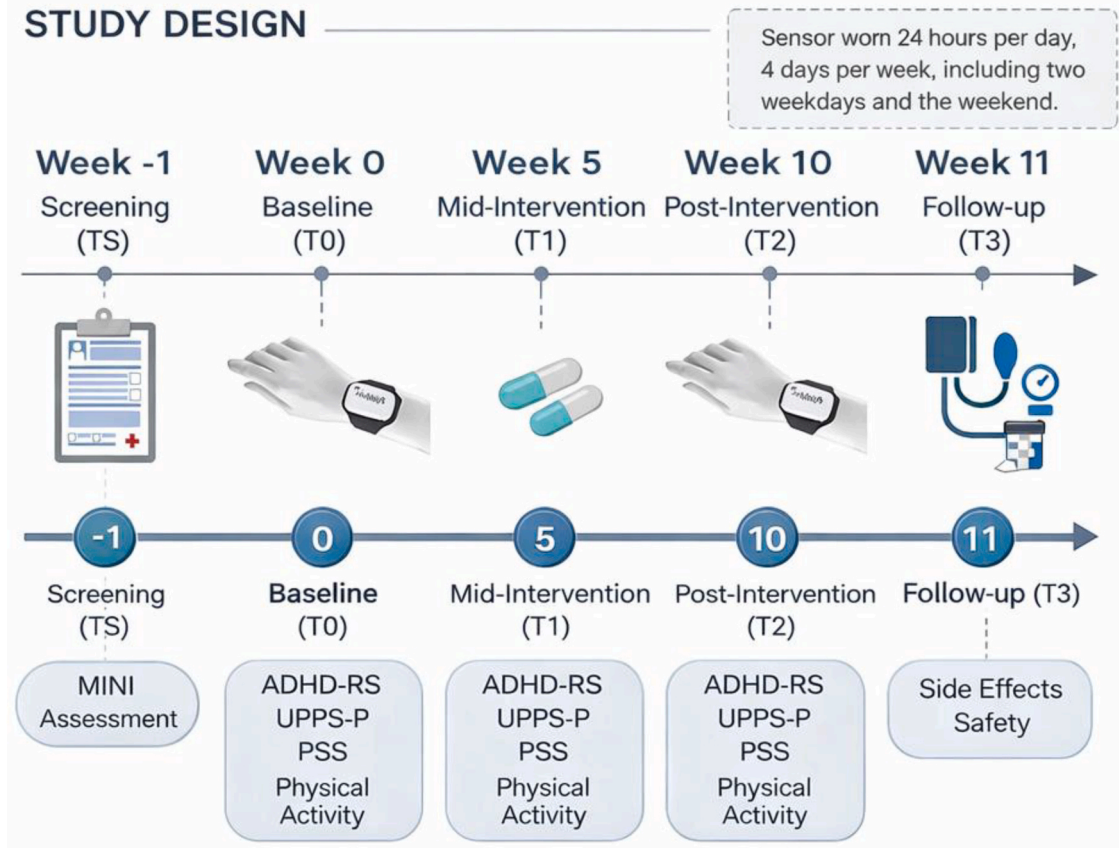


Fig. 1. A Flow-chart of the study. Our analysis involved 155 participants, including 79 with ADHD and 76 healthy controls. Four ADHD participants had no baseline PA data and were excluded from PA analyses resulting in n = 151 (75 ADHD, 76 controls). ADHD = Attention Deficit/Hyperactivity Disorder, Treatment = Synbiotic2000Forte 400. **1B:** Timepoints and data collection, MINI = Mini International Neuropsychiatric Interview, ADHD-RS= Attention Deficit/Hyperactivity Disorder Rating Scale; UPPS-P = Urgency, Premeditation, Perseverance, Sensation seeking, and Positive urgency, PSS = Perceived Stress Scale.

used in this study included movement acceleration (g), total energy expenditure (TEE), and moderate PA (MPA). Movement acceleration was chosen as the most robust measure because it provides a direct and reliable indication of PA levels. TEE and MPA were included to provide a comprehensive understanding of overall energy consumption and to capture different intensity levels of activity. The original sample size requirement for the PROBIA trial was determined based on the primary outcomes of the clinical trial (see (Arteaga-Henríquez et al., 2024)).

2.4. Data preprocessing & categorization

For the present secondary analysis, after applying control filters and minimum wear-time requirements, only participants with valid PA data were included. Daily and four-day mean/SD of PA data were calculated. Movement Acceleration is a PA metric that outputs values that have a very good correlation to the intensity of bodily movements. For each output interval (default is 1min) the values aggregated by calculating the mean value of all samples in the interval. The unit of the output parameter Movement Acceleration Intensity is [g], i.e. multiples of earth gravity ($1g = 9.81 \text{ m/s}^2$). Total energy expenditure is the estimated total expenditure of a person. It is put together by the resting metabolic rate (RMR) and the activity energy expenditure (AEE). RMR is estimated by the WHO equations from age, sex, weight and height. The output parameter TEE has the unit [kcal/day]. PA was categorized as MPA: MET 3–6 (e.g., brisk walking, light exercise).

MPA was sufficiently present in our dataset, but vigorous activity was not analyzed separately because it occurred in few participants ($n = 17$) for few minutes, yielding too few data points for stable estimates. We tested whether combining moderate and vigorous activity changed the results (see [supplementary table R1](#)), but the analyses produced virtually identical results. Light activity was excluded to focus on activity intensities associated with meaningful cardiovascular engagement. Four days of sensor data per period (T0, T2) were used: Participants were asked to wear the sensor over a period of four days, including two weekdays and a weekend for 24 h each day, but any participant with a total of 24 h wear data was included in the analyses. Only data from awake wear-time was considered and missing wear-time data led to exclusion of the dataset. After excluding those without sufficient wear time, or without complete datasets at the time of analysis, 155 participants were initially included (79 ADHD, 76 controls). Four ADHD participants had valid T2 but no baseline PA data and were therefore excluded from baseline PA analyses, resulting in 151 participants (75 ADHD, 76 controls) for PA measures.

To account for inter-individual differences in waking wear time, daily MPA was standardized by each participant's daily wake-wear time. Specifically, for each valid measurement day, MPA minutes were divided by wake-wear time, expressed in hours, yielding MPA minutes per wake-wear hour. This value was then averaged across the four valid measurement days. Thus, the primary standardized MPA variable reflects each participant's average MPA minutes per wake-wear hour, rather than absolute unstandardized MPA minutes. This standardized value was used for all statistical comparisons. For descriptive comparison with the WHO recommendation of 150 min per week, this wear-time-relative value was additionally scaled to a 10-h wake-wear day over 7 days. Primary standardized MPA: mean across up to 4 valid days for (daily MPA minutes/daily wake-wear time in hours). For the WHO comparison: standardized MPA minutes per wake-wear hour $\times 10 \text{ h} \times 7 \text{ days}$. Missing UPPS total scores were not imputed. As previous studies (White et al., 2019) indicate overestimation of Total Energy Expenditure (TEE) and Metabolic Equivalent of the Task (MET), we recalibrated TEE based on movement acceleration and adjusted MET values following established methodologies (Ruf et al., 2021, 2024). The data that support the findings of this study are subject to ethical and legal restrictions and are available from the corresponding author upon reasonable request.

See [supplementary methods](#) and the CONSORT Flow Diagram in

the supplement for details.

2.5. Statistical analyses

2.5.1. Baseline analyses

The Shapiro-Wilk test assessed normality in PA data. Movement Acceleration was not normally distributed in the ADHD group ($p = 0.023$) but was in controls ($p = 0.066$). To normalize the data, Tukey's ladder of power transformations was applied to Movement Acceleration, TEE, and MPA. Post-transformation, all variables met normality assumptions.

Research Question 1 (Group differences in PA): To examine whether PA levels differed between adults with ADHD and neurotypical controls, separate linear regression models were fitted for each PA outcome (Movement Acceleration, TEE, and MPA), with diagnosis (ADHD vs. control) as the independent variable. Age, sex, and BMI were included as covariates in all models. Estimated marginal means were calculated for post-hoc comparisons between groups.

Research Question 2 (PA and symptom severity): To assess whether PA was associated with ADHD symptom severity, Pearson correlations were computed between transformed PA variables and ADHD-RS subscales (inattention, hyperactivity, impulsivity) and impulsivity (UPPS-P) within the ADHD group. Due to non-normal distribution of perceived stress scores, Spearman correlation was used for PSS with untransformed PA variables. Independent samples t -tests compared transformed PA levels between participants with and without comorbid depression (MDD).

2.5.2. Intervention effects

Research Question 3 (PA as moderator of synbiotic intervention): To examine whether PA moderated the effectiveness of synbiotic treatment on ADHD symptom outcomes, separate ANCOVA models were performed for Movement Acceleration, TEE, and MPA, with T2 ADHD-RS ($n = 35$) and UPPS scores ($n = 31$) as dependent variables, baseline scores (T0) as covariate, and treatment group (synbiotic vs. placebo) as the independent variable. Treatment $\times$ PA interaction terms were included to test whether PA moderated intervention effects. Estimated marginal means were used to evaluate synbiotic effects across activity levels.

Research Question 4 (BMI): The effect of synbiotic intervention on BMI was examined using BMI change scores (T2–T0), compared between intervention and placebo groups using an independent samples t -test.

Responder analysis: Participants were classified as responders if they showed $\geq 30\%$ reduction in ADHD-RS or UPPS scores at T2 relative to T0. No UPPS responders were identified; 12 ADHD-RS responders and 23 non-responders were found. Linear regression models assessed differences in PA at T0 and T2 between responders and non-responders, controlling for age, sex, and BMI. Boxplots display the unadjusted distribution of PA variables by responder status for illustrative purposes. Note that responder analyses were exploratory and no power calculation was performed, results should therefore be interpreted cautiously.

In addition, the absence of UPPS responders may arise because ADHD-RS and UPPS-P measure distinct constructs: the ADHD-RS captures ADHD symptoms more broadly, whereas the UPPS-P specifically assesses impulsivity-related symptoms such as urgency, lack of premeditation, lack of perseverance, and sensation seeking (Whiteside & Lynam, 2001), that are considered more trait-like and therefore less amenable to short-term change within a 10-week intervention. It is possible that the reason we do not see an intervention effect is that there is no or just a small effect for impulsivity. In addition, the responder analysis was based on a very small subset of patients and results should be considered with caution.

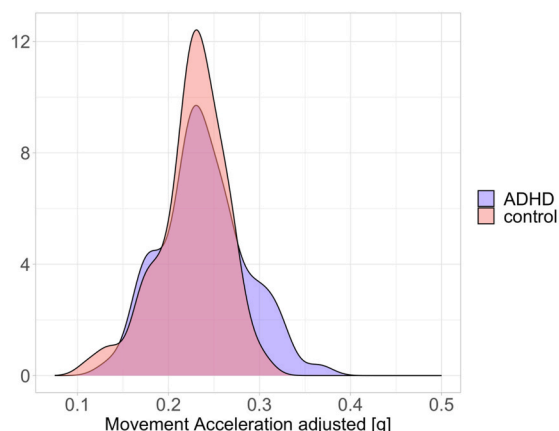
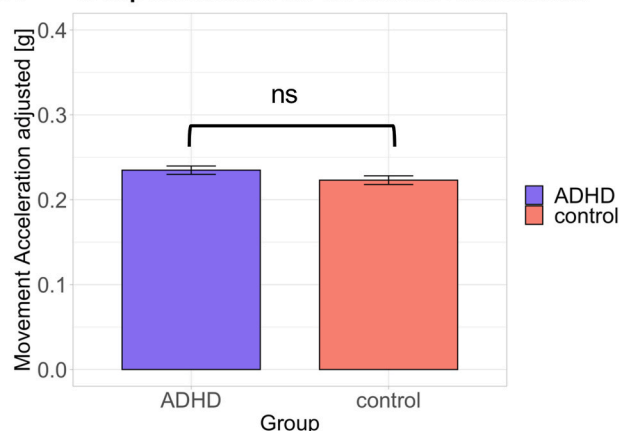
The sample size of the original PROBIA trial was determined based on its primary outcomes. No a priori sample size calculation was performed for the present secondary analysis; instead, a post hoc power

analysis was conducted using repeated measures design with 2 time-points, 2 groups (placebo/intervention) a correlation of 0.5 between measures, $\alpha = 0.05$, and with $f = 0.2$, yielding a total power (1- β probability) of 0.99. Taking into account responders and nonresponders only ($n = 35$) the power would still be sufficient with 0.81.

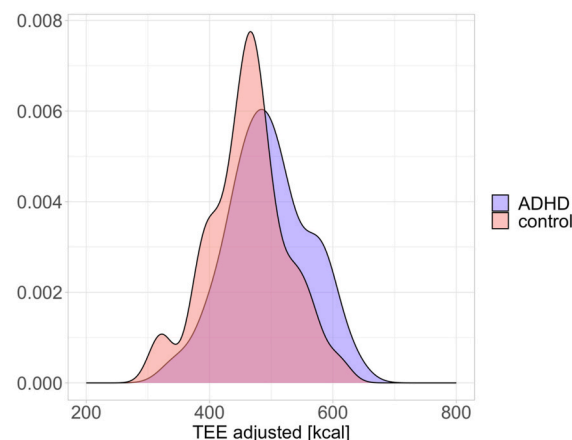
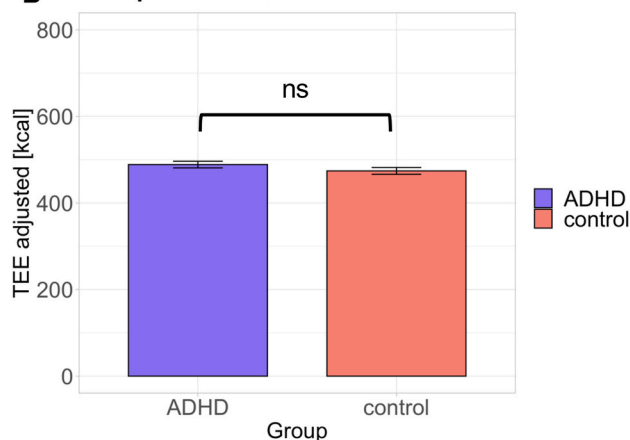
3. Results

After data preprocessing, the final analytical sample contained 79 individuals diagnosed with adult ADHD ($n = 71$) or adult ADHD and Borderline personality disorder combined ($n = 8$) and 76 neurotypical adults as control group. Four ADHD participants had valid T2 but no baseline PA data and were therefore excluded from PA analyses,

A Group differences for Movement Acceleration



B Group differences for TEE



C Group differences for Moderate Activity

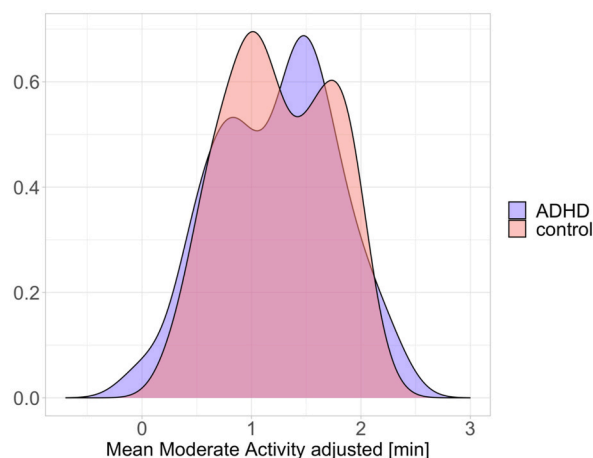
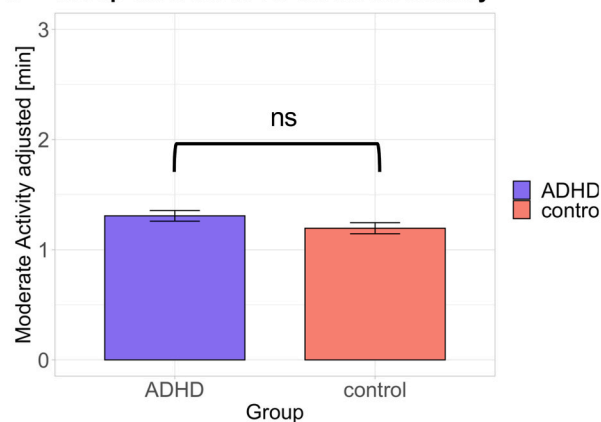


Fig. 2. Group differences between adults without diagnosis and those with an ADHD diagnosis. Results are adjusted for covariates age, sex and BMI. **A.** Movement Acceleration [g]; **B.** Total Energy Expenditure (TEE), **C.** standardized MPA per wake-wear hour [min/h], -ns = non significant; $p < 0.05$ (*). Control $n = 76$, ADHD $n = 75$.

resulting in $n = 151$ (75 ADHD, 76 controls) for these analyses. Participant flow, including losses and exclusions after randomization, has been reported for the full PROBIA trial elsewhere (Arteaga-Henríquez et al., 2020, 2024). Sample sizes vary slightly across analyses due to missing data at specific time points. Exact numbers are reported for each analysis.

3.1. Adults with ADHD do not show differences in the amount of physical activity

To answer the question if adults diagnosed with ADHD are more physically active in everyday life compared to healthy controls, we compared the average movement acceleration (g), total energy expenditure (TEE), and the mean minutes spent in MPA between the two groups. Movement acceleration, TEE and MPA were comparable for patients with ADHD and controls (for g: $b = -0.012$, 95% CI $[-0.027, 0.003]$, $p = 0.119$; for TEE: $b = -14.617$, 95% CI $[-37.5, 8.262]$, $p = 0.209$; MPA: 210 min per week for the ADHD group versus 202 min per week for the control group, $b = -0.113$, 95% CI $[-0.259, 0.033]$, $p = 0.129$). See Fig. 2 for an overview. No statistically significant differences in PA were observed between groups.

3.2. No correlation between PA and symptom severity in adults with ADHD

To assess whether any of the PA indices at baseline correlated with

symptoms of ADHD and symptoms of impulsivity, we analyzed the correlation between average baseline scores of movement acceleration (g), TEE and minutes of MPA. None of the measures correlated significantly with overall ADHD scores (overall ADHD-RS scores: g: $t = 0.911$, $p = 0.365$, $r = 0.107$, $df = 71$; TEE: $t = 1.232$, $p = 0.222$, $r = 0.145$, $df = 71$; MPA: $t = -0.19$, $p = 0.85$, $r = -0.023$, $df = 71$) (see Fig. 3A–C), nor with impulsivity (overall UPPS scores: g: $t = -0.989$, $p = 0.326$, $r = -0.120$, $df = 67$; TEE: $t = -1.484$, $p = 0.142$, $r = -0.178$, $df = 67$; MPA: $t = 0.3$, $p = 0.765$, $r = 0.037$, $df = 67$). Fig. 4A–C gives an overview of the correlations between impulsivity scores and PA indices. We also investigated whether any of the ADHD-RS subscales for inattention, hyperactivity or impulsivity were related to PA. Again, no significant correlation was found (see Supplementary Figs. 1–3). Similarly for the depression and perceived stress scales, no significant association was found with PA indices (for depression: movement acceleration g: $t = 0.206$, $p = 0.839$, TEE ($t = -0.427$, $p = 0.673$), MPA ($t = 1.272$, $p = 0.218$); perceived stress: movement acceleration g ($\rho = -0.019$, $p = 0.872$), TEE ($\rho = 0.021$, $p = 0.856$), MPA ($\rho = -0.085$, $p = 0.469$). See Supplementary Figs. 4 and 5 for an overview.

3.3. PA does not moderate the synbiotic intervention effect

Finally, we examined whether the effects of a synbiotic intervention on impulsivity and overall ADHD scores were influenced by PA. PA parameters at baseline did not significantly influence the ADHD-RS score at T2 (g: $F = 0.83$, $p = 0.371$; TEE: $F = 0.00$, $p = 0.989$; MPA:

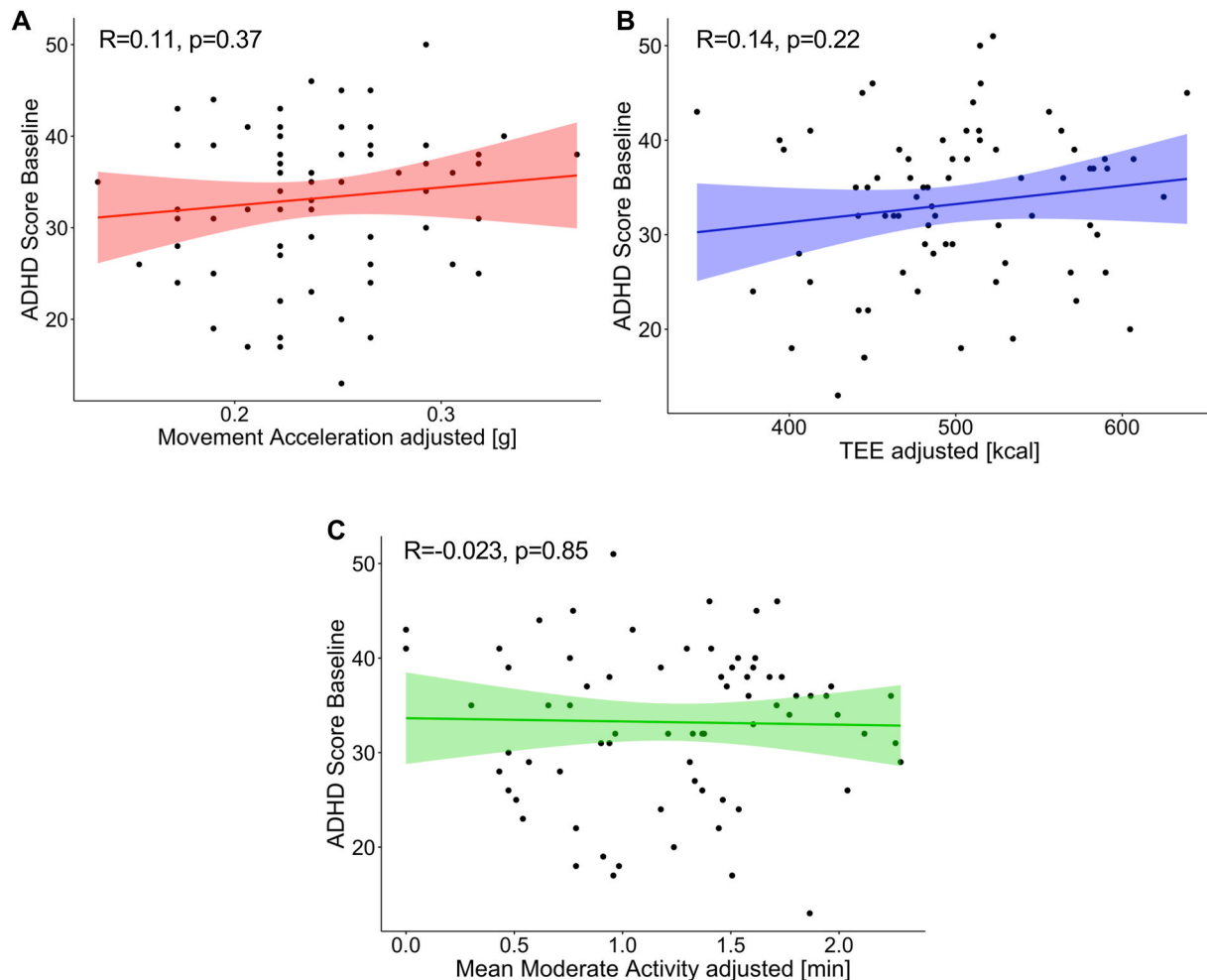


Fig. 3. ADHD Score and PA. Results are adjusted for covariates age, sex and BMI. A. Movement Acceleration [g]; B. Total Energy Expenditure (TEE), C. standardized MPA per wake-wear hour [min/h]. ADHD $n = 73$.

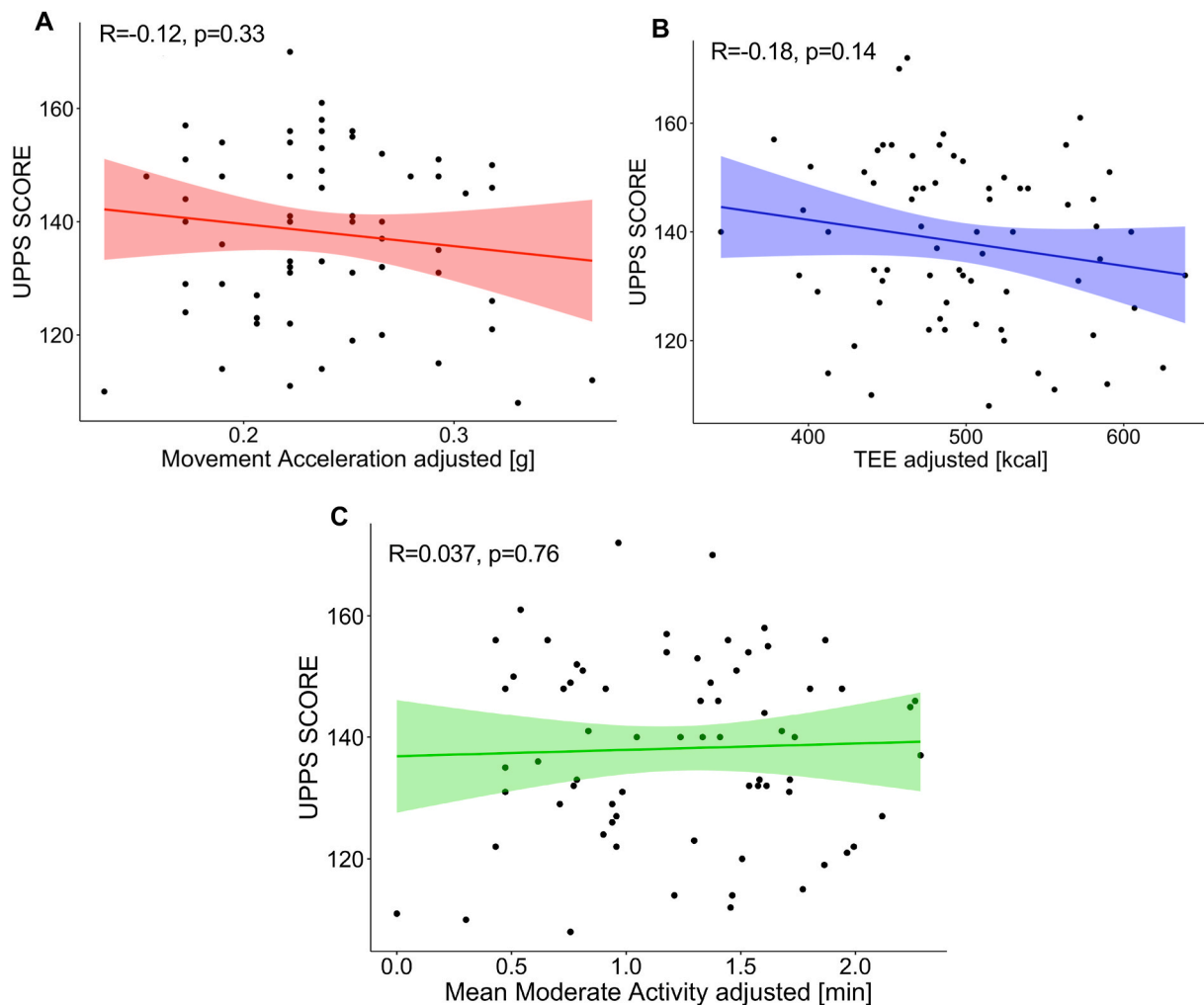


Fig. 4. UPPS Score and PA. Results are adjusted for covariates age, sex and BMI. A. Movement Acceleration [g]; B. Total Energy Expenditure (TEE); C. standardized MPA per wake-wear hour [min/h]. ADHD n = 69.

$F = 0.67$, $p = 0.422$). The estimated mean for our treatment group was 23.5 (SE = 2.40, 95%CI: [18.5, 28.4]). For placebo the estimated mean was 30.6 (SE = 2.82, 95%CI: [24.8, 36.4]). The interaction between PA and treatment did not show significant results (g: $F = 0.39$, $p = 0.536$; TEE: $F = 1.58$, $p = 0.220$; MPA: $F = 1.01$, $p = 0.325$).

We also found no statistically significant effect of PA at baseline on impulsivity scores as measured with the UPPS-P (g: $F = 3.75$, $p = 0.065$; TEE: $F = 0.27$, $p = 0.610$; MPA: $F = 0.1$, $p = 0.755$). The estimated mean change for the treatment group was 149 (SE = 3.01, 95%CI: [142, 155]). For placebo the estimated mean is 141 (SE = 3.56, 95% CI: [133, 148]). No significant effect was found for the interaction between PA and treatment (g: $F = 2.70$, $p = 0.114$; TEE: $F = 0.44$, $p = 0.515$; MPA: $F = 0.04$, $p = 0.841$). See [Supplementary Tables 2 and 3](#) for an overview of all results. In addition, we also investigated whether the often observed decrease of BMI that occurs after a synbiotic intervention was also present in our sample. BMI did not decrease significantly between T0 and T2 ($t = 0.86$, $p = 0.397$).

However, in an additional exploratory analysis, movement acceleration predicted symptom improvement independent of treatment: The analysis showed responders had a higher average movement acceleration (Fig. 5). This effect remained consistent at T2 (movement acceleration: $p = 0.009$, but not TEE: $p = 0.072$, MPA: $p = 0.914$). In summary, this additional analysis suggests that responders generally had higher movement acceleration both before and after the synbiotic intervention, but groups were very small and should be considered with caution. See

[Supplementary Table 4](#) for an overview of all results.

4. Discussion

Our results showed that adults with and without ADHD have similar PA levels, measured across all activity indices. We could not replicate previous findings linking PA or exercise to ADHD severity, nor any specific clinical presentation (i.e., inattention, impulsivity or hyperactivity). In addition, against our hypothesis, PA did not influence outcome for the synbiotic intervention. In a small, exploratory subset, analyses showed that those who responded to treatment - evidenced by improvement in the ADHD Rating Scale - demonstrated significantly higher movement acceleration at both baseline (T0) and post-treatment (T2), but these exploratory analyses should be considered with caution.

In the adults with ADHD, one of the most striking findings was the absence of any association between PA and ADHD diagnosis, ADHD predominant clinical presentations or impulsivity subtypes. This finding highlights that, in addition to the well-documented symptomatic transition in ADHD-such as the shift from hyperactive to more inattentive behaviours in adulthood (Biederman et al., 2000; Cortese et al., 2012)-PA levels also seem to change over time: Considering that young children diagnosed with ADHD are more likely to meet PA recommendations (Bustamante et al., 2019), but this is no longer true by adolescence (Cook et al., 2014; Quesada et al., 2018), our data suggest that there is also no difference in adulthood. While our study is cross-sectional and

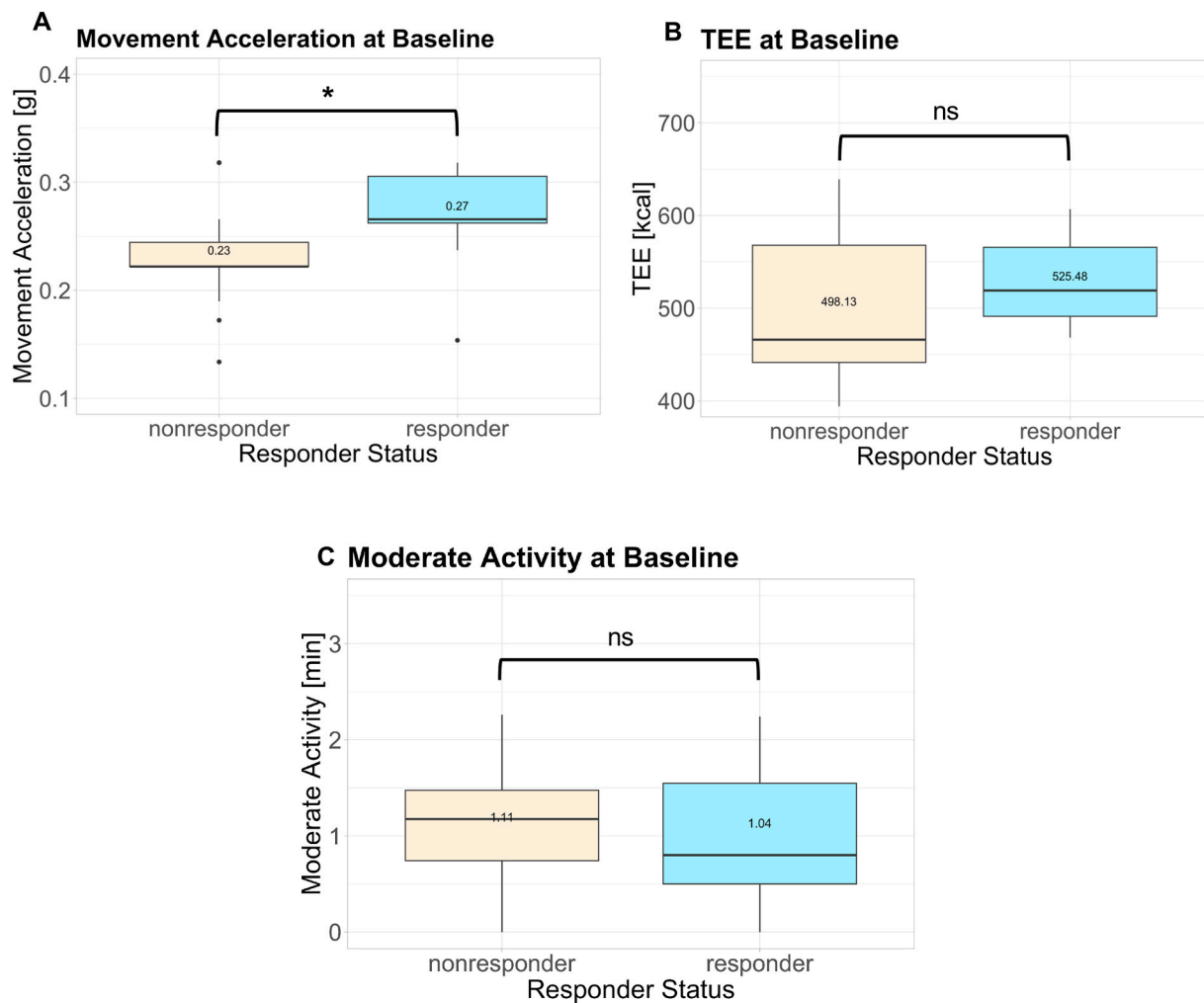


Fig. 5. PA differences at baseline between responders and non-responders. Results are adjusted for covariates age, sex and BMI. **A.** Movement Acceleration [g]; **B.** Total Energy Expenditure (TEE), **C.** standardized MPA per wake-wear hour [min/h]. -ns = non significant; $p < 0.05$ (*). Responders $n = 12$, non-responders $n = 23$.

longitudinal studies could shed light on whether this is truly a shift or influenced by other variables (e.g., type of measurement, improved technology or other confounding variables). Our findings partially contrast with previous research, which has shown differences in some, but not all PA indices among adults with ADHD (Björk et al., 2018; Fritz & O'Connor, 2018). The recent meta-analysis by Dahlberg et al. (Dahlberg et al., 2025), may shed more insight into this relationship: while in adults, acute interventions indeed had a beneficial effect, chronic interventions (i.e., with multiple sessions) did not have an overall effect, although intervention duration did matter, with longer durations showing more beneficial effects. Of note, we here did not investigate interventions (i.e., 'exercise'), but naturally occurring PA, which represents an overall association, not a treatment effect.

Previous research has also suggested that high distractibility, poor time management and a lack of motivation in individuals with ADHD may contribute to the previously reported lower levels of PA (Ogrodnik et al., 2024). In contrast, a recent survey showed that adults with ADHD were motivated to spend a considerable amount of time exercising to achieve symptom relief (Cochrane et al., 2022). Additionally, one of the studies reporting a significant difference has shown that when factors such as education and income are accounted for, differences in PA levels between adults with and without ADHD are no longer observed (Björk et al., 2018).

Though not recommended as stand-alone treatment, it is possible that adults with ADHD have been advised to be more physically active

during their course of treatment, and this could have increased general PA levels in our population. Exercise is often recommended in treatment guidelines as part of a healthy lifestyle (Kazdin, 2000; Muth, 2020) and several studies support its beneficial effect for mood regulation and symptoms of inattention (Abramovitch et al., 2013; Chang et al., 2012; Fritz & O'Connor, 2016; Koch et al., 2022; Mehren et al., 2019). A recent umbrella review with meta-analysis analyzed the evidence available and showed that exercise improves inattention, inhibitory control, and cognitive flexibility, but found no evidence for improved hyperactivity and/or overall behavioral functioning (Dastamooz et al., 2023). Again, it should be noted that the meta-analysis included studies with a specific intervention, which, per definition, is different from PA and likely produced stronger effect sizes compared to the natural variations in PA examined in our study. This difference may explain why we did not find a correlation between ADHD symptoms and PA.

Evidence is less clear for adults than for children, but data indicates that exercise still plays a major role in reducing ADHD symptoms and improving quality of life in adults with ADHD (Berger et al., 2014; Fritz & O'Connor, 2016; Gapin et al., 2015; Mehren et al., 2019), and is linked to a more positive affect (Koch et al., 2022). The World Health Organization (WHO) recommends that adults engage in either 150 to 300 min of MPA, and/or 75 to 150 min of vigorous activity per week (World Health Organization, 2020). In our study, the mean for the ADHD group when standardizing for 10-h wake-wear time, was 210 min of MPA (SD = 217.68) per week, which was comparable, if slightly lower

in the control population (202 min, SD = 190.38), indicating that our sample reached the recommended treatment guidelines.

4.1. No moderating effect of PA on the Synbiotic intervention

We found no evidence that the synbiotic intervention moderated the relationship between PA and changes in ADHD symptoms, suggesting that, in the present sample, PA and synbiotic supplementation did not exert synergistic effects on ADHD outcomes.

This finding is noteworthy for several reasons. First, both PA and, although less extensively studied, probiotics, prebiotics, and synbiotics have been suggested to positively influence ADHD symptoms (see Introduction section). However, the possibility that these interventions interact has not, to our knowledge, been formally investigated. Explicitly testing this moderation, we found no evidence supporting such an effect.

It is also possible that negative moderation findings (for ADHD or other outcomes) are underreported (e.g., as a form of publication bias), making the existing literature less representative of the true pattern of results. Several alternative explanations for the absence of a detectable interaction should be considered. Although this study was embedded within a relatively large clinical trial, the sample size available for the moderation analyses was still modest, limiting statistical power to detect small interaction effects. Thus, a true but small moderating effect cannot be ruled out. Furthermore, the beneficial effects observed in the primary analyses of this trial (Arteaga-Henríquez et al., 2024) were themselves relatively modest, which may have constrained the potential to detect synergistic effects between PA and synbiotic supplementation.

It is also possible that PA and synbiotics influence ADHD symptoms through largely independent mechanisms, resulting in additive rather than interactive effects. Alternatively, the timing, intensity, or duration of the interventions may not have been sufficient to produce detectable synergistic effects. Finally, heterogeneity of individual responses to both PA and synbiotic supplementation may have obscured interaction effects at the group level.

Only in our small subsample for the exploratory analyses, responders to the synbiotic therapy (as defined by a 30% reduction in the ADHD Rating Scale) showed significantly higher PA (movement acceleration) both at baseline and T2. Our findings raise the question of why PA might have a beneficial effect on ADHD symptoms, even in the absence of direct associations with hyperactivity or impulsivity levels. These results should be considered with caution, particularly since the continuous analyses showed no association between baseline PA and ADHD symptoms. It could be speculated that the improvement in ADHD symptoms in responders is more closely related to general levels of physical activity. However, this hypothesis should be tested in larger datasets, as the analysis was exploratory and not designed to detect such effects.

4.2. Strengths and limitations

We can note several strengths of our study: First, we assessed PA using objective measurements. Additionally, our sample size is relatively large, and ADHD diagnoses in adults were thoroughly and carefully verified using a standardized interview.

Several limitations should be considered when interpreting our findings. First, our study was exploratory and used only a subset of participants with available data of the PROBIA trial. Furthermore, the estimation of PA and in particular minutes spent doing activity is likely overestimated, despite using corrections for wearing the sensor on the wrist. Given that we opted to include the maximum of available data, participants had to wear the sensor for at least 24 h over a period of 4 days. The standardization method used for MPA (see section 2.4) deviates somewhat from previously used methods (i.e., using the wear time as covariate). A limitation of this approach is that the standardized MPA variable does not represent absolute daily MPA minutes. Instead, it represents MPA expressed relative to wake-wear time, calculated as

average MPA minutes per wake-wear hour across the valid measurement days. Therefore, the results should be interpreted as relative, wear-time-standardized MPA rather than total daily MPA. Within our sample, the group comparisons remain valid, but the estimates of minutes spent doing MPA should be considered cautiously. The included ADHD sample represents a specific subgroup of participants from the PROBIA trial and may therefore not be representative of the broader adult ADHD population. In particular, the inclusion of a small number of individuals with comorbid borderline personality disorder further limits generalizability. Additionally, the present study was a secondary analysis of the PROBIA trial, which was not powered for the current research questions, in particular the responder analysis was conducted in a very small sample ($n = 12$ responders). Finally, only a subset of patients included in the original trial had PA data available and we were not able to perform the analysis on the original definition of responders/non-responders.

4.3. Conclusion

Our study is among the first to use an objective, naturalistic measure of PA in adults with ADHD. In contrast to previous findings in children, we did not find differences here in PA between adults with ADHD and controls. In adults with ADHD, objectively measured PA did not correlate with symptoms of inattention, hyperactivity and impulsivity, nor did it amplify the response to a synbiotic intervention. Future studies should assess PA levels in adults with ADHD objectively and determine whether improved symptomatology can be found in adults reaching recommended levels of PA following the WHO guidelines.

CRediT authorship contribution statement

Hannah Marie Schulz: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Alea Ruf:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Anne Siegl:** Writing – review & editing, Writing – original draft, Data curation. **Gara Arteaga-Henríquez:** Writing – review & editing, Writing – original draft, Data curation. **Carolina Ramos-Sayalero:** Writing – review & editing, Writing – original draft, Investigation. **Tünde Kilencz:** Writing – review & editing, Writing – original draft, Data curation. **István Bitter:** Methodology, Writing – original draft, Writing – review & editing, Funding acquisition. **Clara Hausmann:** Writing – original draft, Methodology, Formal analysis. **Ulrich Ebner-Priemer:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **János M. Réthelyi:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition. **Andreas Reif:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Josep Antoni Ramos-Quiroga:** Writing – review & editing, Writing – original draft, Funding acquisition. **Silke Matura:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Carmen Schiweck:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Ethics declaration

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

This study included organ or tissue donors. This study includes human biological material and consent was obtained by donors, or their next of kin or legal representatives, for use in this study and for publication of the article. The samples used in this research were not sourced from executed prisoners or prisoners of conscience.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This

study was approved by the Goethe University Hospital Frankfurt in Germany, Semmelweis University via the Ministry of Human Capacities in Hungary, and the University Hospital Vall d'Hebron in Barcelona, Spain. (Approval No. Frankfurt: 269/18; Barcelona: 311/2018; Semmelweis: Issued by the Ministry of Human Capacities for the study protocol requested at Semmelweis University 03 SEP 2019)

The results of this clinical trial and any associated work have been posted in a registry. This clinical trial was registered with number NCT03495375 (clinical trials gov).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author xxxx (to be added after peer review process to keep anonymity intact as per journal requirement) used ChatGPT to improve the language and readability of the manuscript. After using this tool, the author carefully reviewed and edited the content and takes full responsibility for the published article.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andreas Reif, J. Antoni Ramos-Quiroga report financial support was provided by European Commission. Andreas Reif reports a Relationship with Medice, Shire/Takeda, SAGE/Biogen, Janssen, Boehringer Ingelheim and cycleron that includes: consulting or advisory and travel reimbursement. Istvan Bitter reported receiving consulting fees from Gedeon Richter and Janssen/Janssen-Cilag; speaker's honoraria from Gedeon Richter, Hikma Pharmaceuticals, Janssen/Janssen-Cilag, KRKA, Lundbeck, and Medichem Pharmaceuticals Inc. by Unilab; research grant from Gedeon Richter; royalties from Oxford University Press. J. Antoni Ramos Quiroga reports a relationship on the speakers' bureau and/or acted as consultant for Biogen, Idorsia, Casen-Recordati, Johnson&Johnson, Novartis, Takeda, Bial, Sincrolab, Neuraxpharm, Novartis, BMS, Medice, Rubió, Uriach, Technofarma and Raffo in the last 3 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Idorsia, Johnson&Johnson, Rubió, Takeda, Bial and Medice. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 3 years: Exeltis, Idorsia, Neuraxpharm, Oryzon, Roche, Probitas and Rubió. Johnson&Johnson. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mhpa.2026.100824>.

Data availability

Data will be made available on request.

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