Author(s): Rodriguez-Ayllon, María; Neumann, Alexander; Hofman, Amy; Voortman, Trudy; Lubans, David R.; Yang-Huang, Junwen; Jansen, Pauline W.; Raat, Hein; Vernooij, Meike W.; Muetzel, Ryan L.

Title: Neurobiological, Psychosocial, and Behavioral Mechanisms Mediating Associations Between Physical Activity and Psychiatric Symptoms in Youth in the Netherlands

Year: 2023

Version: Accepted version (Final draft)

Please cite the original version:

Rodriguez-Ayllon, M., Neumann, A., Hofman, A., Voortman, T., Lubans, D. R., Yang-Huang, J., Jansen, P. W., Raat, H., Vernooij, M. W., & Muetzel, R. L. (2023). Neurobiological, Psychosocial, and Behavioral Mechanisms Mediating Associations Between Physical Activity and Psychiatric Symptoms in Youth in the Netherlands. JAMA Psychiatry, 80(5), 451-458. https://doi.org/10.1001/jamapsychiatry.2023.0294

The neurobiological, psychosocial and behavioral mechanisms linking physical activity with psychiatric symptoms in young people: a longitudinal population-based study.

María Rodriguez-Ayllon[1], PhD; Alexander Neumann[2,3], PhD; Amy Hofman[1], MSc; Trudy Voortman[1,6], PhD; David R Lubans[7,8,9], PhD; Junwen Yang-Huang[10], PhD; Pauline W. Jansen[4,5], PhD; Hein Raat[8], MD, PhD; Meike W. Vernooij[1,11*], PhD; Ryan L. Muetzel[4], PhD.

[1]Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, the Netherlands.
[2]Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium.
[3]VIB Center for Molecular Neurology, Antwerp, Belgium.
[4]Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC University Medical Center Rotterdam, the Netherlands.
[5]Department of Psychology, Education and Child Studies, Erasmus University Rotterdam, Rotterdam, the Netherlands.
[6]Division of Human Nutrition and Health, Wageningen University & Research, the Netherlands
[7]Centre for Active Living and Learning, University of Newcastle, Australia.
[8]Hunter Medical Research Institute, New Lambton Heights, New South Wales, Australia
[9]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland.
[10]Department of Public Health, Erasmus Medical Center, Rotterdam, Netherlands.
[11]Department of Radiology and Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands.

Word count:

Manuscript: 3000

Date of the revision: 14th December 2022

*Corresponding Author
Meike Vernooij
Department of Radiology and Nuclear Medicine, Department of Epidemiology
Erasmus MC University Medical Center
P.O. box 2040
3000 CA, Rotterdam, the Netherlands
m.vernooij@erasmusmc.nl
Direct dial: +31(0)107034033

SUMMARY

Importance: Understanding the mechanisms linking physical activity with a lower risk of psychiatric symptoms may stimulate the identification of cost-efficient strategies for preventing and treating mental illness at early life stages.

Objective: To examine the neurobiological, psychosocial, and behavioral mechanisms linking physical activity with psychiatric symptoms in youth by testing an integrated model.

Design, setting, and participants: Generation R is a prospective, population-based cohort study that collects data from fetal life until young adulthood in a multi-ethnic urban population. Data were analyzed from 4,216 children (6.0±0.4 years at visit 1; 50.2% girls) at 3 time points: 6, 10 and 13 years.

Exposure(s): Physical activity was ascertained at age 6 (visit 1) via parent-report and included weekly frequency and duration of walking or cycling to/from school, physical education at school, outdoor play, swimming, and sports participation.

Main outcome(s) and Measure(s): Psychiatric symptoms (internalizing and externalizing symptoms) were assessed at age 6 (visit 1) and at age 13 (visit 3) using the Child Behavior Checklist. Several mechanisms, measured at the age of 10 (visit 2), were explored as mediators. Neurobiological mechanisms included total brain volume, white matter microstructure, and resting-state connectivity assessed using a 3T MRI scanner. Psychosocial mechanisms included self-esteem, body image, and friendship. Behavioral mechanisms included sleep quality, diet quality, and recreational screen time.

Result(s): More sports participation was associated with fewer internalizing (β_{direct}=-0.025, standard error (SE)=0.078, p=0.031) but not externalizing symptoms. Self-esteem mediated the relationship between sports participation and internalizing symptoms ($\beta_{indirect}$=-0.009, SE=0.018, p=0.002). No evidence was found for associations between any other neurobiological, psychosocial, and behavioral variables linking sports with psychiatric symptoms. No association was found between other types of physical activities and psychiatric symptoms at these ages.

Conclusions and Relevance: This integrated model provides an overview of the mechanisms linking physical activity with psychiatric symptoms in youth. We observed that self-esteem

mediated the modest association between sports participation in childhood and internalizing problems in adolescence. Further studies might explore whether larger effects are present in certain subgroups (e.g., children at high risk of developing psychiatric symptoms), different ages, or structured sport-based physical activity interventions.

Key Points

Question: Which neurobiological, psychosocial, or behavioral pathways mediate the associations between physical activity and psychiatric symptoms in young people?

Findings: Our integrated model suggests that psychosocial mechanisms (i.e., self-esteem) mediate the association between sports participation in childhood and internalizing symptoms in adolescence.

Meaning: Physical activity interventions carried out during childhood should consider self-esteem improvements as a channel to protect young people against the later emergence of internalizing problems.

INTRODUCTION

The transition from childhood to adolescence involves extensive developmental changes, which coincide with an increased vulnerability to psychiatric symptoms[1]. Risk factors for psychiatric symptoms have been well established[1]. However, less is known about the protective factors for psychiatric symptoms in youth.

Compelling evidence demonstrated that physical activity positively affects mental health from childhood to adulthood[2–5]. The strength of the evidence has led the World Health Organization to include psychiatric symptoms such as depression and anxiety among the conditions which can be prevented through physical activity in their most recent guidelines[4,6]. However, the pathways between physical activity and mental health and the life stage at which these come into play remain unknown. In this context, Lubans et al.[7] suggested a conceptual model which postulates three broad categories of mechanisms through which physical activity potentially acts on mental health: neurobiological, psychosocial, and behavioral mechanisms.

The neurobiological mechanism hypothesis suggests that physical activity may alter brain structure or function, and in turn, reduce the development of psychiatric symptoms[8,9]. For instance, depression has been linked to a lower density of neuronal cells in the hippocampus[10,11], a region that showed structural plasticity in response to physical activity[8]. Higher physical activity has also been associated with better white matter microstructure during childhood[12]. Nevertheless, it is unknown whether changes in white matter mediate the effect of physical activity on psychiatric symptoms.

The psychosocial mechanism theory proposes that physical activity might satisfy basic psychological needs, such as social connectedness, which in turn could decrease the risk of developing psychiatric symptoms in youth[13]. Extensive research has also shown the effect of physical activity on psychiatric symptoms is partially mediated by changes in the perception of the self[14].

Lastly, changes in psychiatric symptoms resulting from physical activity could be also mediated by changes in associated behaviors, such as improved sleep, healthier eating habits or reduced recreational screen time[15].

Overall, some isolated mechanisms through which physical activity may reduce psychiatric symptoms have been identified[13,16]. Nevertheless, an integrated model examining the joint and independent contributions of the proposed mechanisms is lacking, making it difficult to obtain a comprehensive picture. We hypothesize that its effects on psychiatric symptoms operate via multiple mechanisms, rather than a single one. Therefore, the aim of our study was to identify key mechanisms responsible for the effects of physical activity on psychiatric symptoms in youth, using an integrated perspective[17].

METHODS

Study design and participants

This study was part of the *Generation R Study*, a prospective population-based birth cohort conducted in Rotterdam, the Netherlands. The design is detailed elsewhere[18,19]. Briefly, around 10,000 pregnant women from the general population were enrolled in the study between 2002 and 2006 and data have been collected from them and their children over the past 20 years[18,19]. The current study used data from children at 3 time points around their ages of 6, 10, and 13 years. The Medical Ethics Committee of Erasmus Medical Centre approved all study procedures. All participants provided written informed consent/assent. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[20] guidelines were followed (**Supplemental Material 1**).

Sample

At the age of 6 years, 6,265 participants provided physical activity data (exposures). Of these, 4,216 participants provided data on psychiatric symptoms as well (outcomes) at the age of 13 years and thus have complete data on both exposure and outcome (**Figure S1**).

Study variables

Physical activity

Physical activity was reported by the primary caregiver (97% mothers). The questionnaire included frequency and duration that a child engaged in: physical education at school, walking or cycling to/from school, outdoor play, swimming, and sports (i.e., athletics, basketball, combined sports, dance, football, gymnastics, hockey, martial arts, tennis, others)[12]. Time spent on each activity was calculated as (days per week)*(hour per day). Total physical activity was calculated by adding the hours of active commuting, physical education at school, outdoor play, swimming, and sport participation.

Psychiatric symptoms

Primary caregivers filled out the validated Child Behavior Checklist (CBCL) to report on children's psychiatric symptoms[21,22]. We examined the CBCL broadband subscales of internalizing problems (i.e., depression, anxiety, somatic symptoms) and externalizing problems (i.e., conduct problems, rule-breaking behavior, attention-deficit/hyperactivity problems) as well as the 6 Syndrome Scale subdomains.

Neurobiological mediators

High-resolution structural magnetic resonance imaging (MRI), diffusion weighted white matter imaging (DTI), and resting-state functional MRI were collected on a 3T MRI[23]. Structural MRI data were processed through FreeSurfer[23], which yielded anatomical labels for broad tissue classes (e.g., white and gray matter) and several brain structures (e.g., hippocampus). Diffusion image preprocessing was conducted using the FMRIB Software Library (FSL)[24]. Two metrics of white matter microstructure (i.e., fractional anisotropy [FA] and mean diffusivity [MD]), were derived globally (e.g., across multiple tracts) and for corpus callosum fibers (the forceps major and minor). Dynamic functional network connectivity was estimated using the Group ICA Of fMRI Toolbox (GIFT)[25].

Psychosocial mediators

This study analyzed: self-esteem (individual´s evaluation of their qualities and limitations) using an adapted 18-item question format of the Harter's Self Perception Profile for Children[26]; body image (perceived physical attractiveness) using the Development of the Children's Body Image Scale[27]; and friendships (a state of mutual trust and support between people) using an adapted version of the Friendship Quality Questionnaire (FQQ; Parker and Asher 1993)[28,29].

Behavioral Mediators

Sleep quality was evaluated using the Sleep Disturbance Scale for Children[30,31]. Higher scores indicate lower sleep quality. Diet quality was quantified by a predefined food-based diet quality score, based on Dutch dietary recommendations for 8-year-old children[32]. Recreational screen time was obtained through a parent-reported questionnaire[19].

See the **Supplemental Material 2** for further details.

Confounders

Parental education and national origin, and child age, sex, body mass index (BMI) and non-verbal intelligence quotient (IQ) were included as confounders. Parental national origin was based on the country of birth of the mother and mother's parents and was ascertained via questionnaire with categories conforming to those used by the Dutch Government Office for Statistics. Parental education was defined by the highest completed education and divided into 2 categories ranging from low (from no education to high school or vocational training) to high education level (from higher vocational education to university). Child height and weight were measured at the research center and body mass index (BMI) was calculated and standardized according to the Dutch reference growth curves (https://growthanalyser.org)[33]. A non-verbal intelligence quotient (IQ) was assessed using the *Snijders-Oomen Niet-verbale intelligentie Test- Revisie (SON-R 2.5–7)*[34].

Statistical analyses

Statistical analyses were performed using R Statistical Software (version 4.0.5)[35]. First, we explored the Pearson´s correlation between physical activity measures and psychiatric symptoms, with false discovery rate (FDR) correction applied to account for the number of tests performed[36]. Second, mediation analyses were performed with the Lavaan package (Version 0.6-9)[37] when a correlation (p_{FDR} <0.05) between exposure and outcome was observed. Physical activity was entered into the model as the exposure, and the neurobiological, psychosocial, and behavioral mechanisms were entered as mediators. Specifically, we explore the individual role of each mediator in the relationship between physical activity and psychiatric symptoms. Additionally, we grouped individual mediators into three categories (i.e., neurobiological, psychosocial, and behavioral) according to a previously proposed conceptual model[7], and explored its summed indirect effect on the relationship between physical activity and psychiatric symptoms. Lastly, psychiatric symptoms indexed as broadband scales of internalizing symptoms and externalizing symptoms, were entered as outcomes. An illustration of the general modeling strategy is depicted in **Figure S2**. Mediation models were adjusted for several potential confounders, including baseline psychiatric symptoms at age 6, and parent's education level, national origin, child sex, age at visit 1, BMI, and IQ. Additionally, we tested whether the mediation mechanisms differed between (i) girls and boys, (ii) children from different parental education, (iii) children with different BMI, by performing mediation invariance analyses (multi-group analyses). Lastly, a number of supplemental and sensitivity analyses were run (see **Supplemental Material 2**).

Maximum likelihood with robust standard errors (MLR) was used to fit the structural equation models, while accounting for missing data in mediators and confounders (full-information ML), as implemented in Lavaan[37]. This is a standard approach to prevent listwise deletion of participants with missing data.

RESULTS

Sample characteristics

The mean age of the study population was 6.0 ± 0.4 years at baseline, 9.8 ± 0.3 at visit 2, and 13.5 ± 0.4 at visit 3 (**Table 1**). 50% of the participants were girls. Characteristics of participants with complete cases in predictors, outcomes, and mediators are shown in **Table S1**. Descriptive information on exposures, mediators, and outcomes is presented in **Table S2**. At baseline, participants reported a total physical activity of 14.6±8.1 hours per week. Compared to sports participation (0.6 ± 0.8 hours per week), the levels of outdoor play were relatively high (11.2 ±7.9 hours per week). Non-response information to ascertain how similar the study sample is to the original cohort is shown in **Table S3**.

Correlation between physical activity and psychiatric symptoms

A correlation matrix of physical activity and psychiatric symptoms is presented in **Figure 1**. Higher levels of sports participation at age 6 were correlated with lower levels of internalizing symptoms at age 13 ($r=-0.063$, $p_{adjusted}=0.001$). No other correlations were observed for other measures of physical activity and psychiatric symptoms. Therefore, mediation analyses were only carried out with sports participation as the predictor and internalizing symptoms as the outcome, see **Figure S2**.

Mediation analyses

The results of the overall integrative mediation model is presented in **Figure 2**. Higher levels of sports participation were associated with lower internalizing symptoms ($\beta_{direct}= -0.025$, standard error (SE)= 0.078, $p=0.031$). From all mediators, only self-esteem mediated the association between sports participation and internalizing symptoms ($\beta_{indirect}= -0.009$, SE= 0.018, $p=0.002$). Specifically, self-esteem explained 26% of the variance ($\beta_{indirect}/\beta_{total\ effect}$) in the relationship between sports participation and internalizing symptoms. Independently, higher levels of sports participation were associated with higher self-esteem ($\beta=0.059$, SE=0.084, $p<0.001$), and higher self-esteem was associated with lower internalizing symptoms ($\beta= -0.146$, SE=0.027, $p<0.001$). In a post-hoc exploratory analysis, we detected the mediating role of self-esteem was mainly driven by the athletic competence domain (see **Figure S3**).

Independently, higher sports participation was associated with a better diet quality (β=0.049, SE=0.028, p=0.011), while lower sleep quality was associated with higher internalizing symptoms (β=0.082, SE=0.041, p<0.001).

Multi-group analyses showed no differences between girls and boys (p_{Chisq}=0.179), and between children with different BMIs (p_{Chisq}=0.242). In contrast, we found differences between children from families with lower versus higher educational status (p_{Chisq}<0.001). In our stratified analyses, self-esteem mediated the effect of sports participation on internalizing problems among those with lower levels of parental education ($\beta_{indirect}$=-0.019, SE=0.035, p=0.002), but not among those with higher levels of parental education ($\beta_{indirect}$=-0.004, SE=0.017, p=0.209). See **Figures S4-S5** for further details. Several additional supplemental analyses were run to examine the specificity and sensitivity of the results (e.g., specific psychiatric symptoms) and are presented in the supplement (**Supplemental Material 3**).

DISCUSSION

In this study, we sought to shed new insights into the relationship between physical activity and mental health in youth. Specifically, using in-depth neurobiological, psychological, and behavioral measures gathered from a large, representative sample of over 4,000 youth, we observed that self-esteem mediated the association between sports and internalizing symptoms in youth. Thus, more participation in sports was related to increased self-esteem which in turn was related to lower levels of internalizing problems at follow-up, independent of baseline mental health status. This finding was particularly relevant in children whose caregivers did not pursue higher education.

Sports participation was inversely associated with internalizing symptoms in youth. However, this association was relatively small. The magnitude of associations in this study are in line with previous studies[5,38–41]. For instance, involvement in sports during childhood was negatively associated with depressive symptoms in young adulthood; however, the association was small, especially after including potential confounders[41]. Additionally, research has argued that in trials with controlled, clinical samples, physical activity has a larger and more beneficial effect on psychiatric symptoms in comparison to studies involving the general population[39]. Taken together, these findings suggest that larger effect sizes might be observed in studies including clinical samples of adolescents diagnosed with major psychological disorders[38–40]. Lastly, we did not observe associations between other types of physical activities and psychiatric symptoms, which suggests that practicing sports during early childhood might be the most effective physical activity practice to improve or preserve adolescents´ mental health.

Self-esteem (i.e., how one feels about their abilities and limitations[42]) mediated the association between sports and internalizing symptoms in youth. Adolescents shape their self-esteem by developing skills, discovering preferences, and associating themselves with others[43]. Sports activities offer youth a means to develop their self-esteem, distinguish themselves from others, and a challenging setting outside of academics[43]. Therefore, it is possible that early participation in sports could provide children with a more mature self of themselves during adolescence, which might help them to deal with new life circumstances (e.g., academic pressure or the influence of peers), and protect their mental health. This finding is consistent with our recent systematic review where we observed self-dimensions were the only consistent paths through which physical activity reduces psychiatric symptoms in youth[44].

The mediating role of self-esteem was mainly driven by the athletic competence domain, referring to one´s ability to do well at sports. These results further support the idea that youth with high perceived competence in sports are more likely to enjoy and experience the positive effects of sports on mental health[45]. Consequently, future sports-based interventions designed to protect young people's mental health might consider the use of evidence based-physical activity strategies (e.g., the SAAFE principles)[46], as well as considering young people´s sports preferences[47].

Self-esteem mediated the association between sports participation and internalizing symptoms, particularly among children of low-educated caregivers. Home environments, low parental education, or low socioeconomic status can act as early life adversities in the context of emerging psychiatric problems in childhood[48–50]. However, some children in the same circumstances may be more resilient to the development of psychiatric symptoms. This fact could be partially explained by the interaction of intrapersonal resilience factors such as IQ, self-identity, or self-esteem[50]. Specifically, self-esteem has been identified as a potential mediator in the relationship between early life adversities and the development of psychiatric symptoms[51]. Notably, self-esteem could be improved by effective sport-based interventions[52,53]. Therefore, future studies should explore whether improving self-esteem through early sports based-interventions may protect the overall mental health of youth exposed to early life adversities.

We did not observe any other mechanisms linking sports participation with internalizing symptoms. Accordingly, our systematic review showed the role of the neurobiological mechanisms in the relationship between physical activity and psychiatric symptoms is unclear, probably because of the inconsistencies and heterogeneity observed among studies[44]. For instance, previous studies have used MRI data as indicators of the neurobiological mechanisms while others have examined the role of blood circulating biomarkers[44]. In healthy young individuals, neurobiological measurements in the form of circulating blood biomarkers might offer a more dynamic indication of the role of neurobiological mechanisms in the relationship between physical activity and psychiatric symptoms. Specifically, a 20-week physical exercise intervention reduced the levels of the circulating macrophage scavenger receptor type-I (MRS1) in children[54]. MRS1 is a membrane glycoprotein expressed in macrophages and has been associated with neurobiological processes and neurological diseases[55]. In contrast, the same intervention did not affect the structural and functional brain outcomes explored[56]. Other potential reasons, such as neurodevelopmental differences between the children, the need for more advanced imaging methods, or the whole brain vs. region-specific approach, could be clouding the potential role of neurobiological mediators in this relationship. Lastly, future studies should explore other psychosocial (e.g., enjoyment) and behavioral (e.g., coping skills) mechanisms.

Strengths and Limitations

We used data across 3 time points from one of the largest cohorts of youth with information on physical activity, behavioral and emotional measures, and neuroimaging worldwide. A strength of this study was the unique inclusion of a broad set of mechanisms into a previously described integrated model that allowed us to obtain an overall picture of the mechanisms linking physical activity with psychiatry symptoms in youth. Further, the prospectively-collected data across different points in time allowed us to model these mechanisms within a mediation framework. Nonetheless, our findings must be interpreted in the context of relevant limitations. First, the observational design limits inferences about causality to any of the associated factors, and residual confounding cannot be ruled out. Second, other potential mechanisms not included in the model could also mediate the association between sports and psychiatry symptoms. Third, we studied the mechanisms underlying the long-term associations of sports with psychiatry symptoms from childhood to adolescence. It is possible, that more immediate effects of sports on psychopathology, e.g. within days or months, act via different mediators, which could be explored in future research using more high-frequency repeated measures. Fourth, we measured, only at a single time point, the predictor and the mediators, which did not allow us to explore the stability of those variables from childhood to adolescence. Similarly, the precise reliability of some self-reported mediators at such a young age remains unclear. Fifth, physical activity was assessed by parental reports, leading to the possibility of under- or overestimations of the behaviors.

Additionally, both the predictor and the outcome were reported by the primary caregivers, which could overestimate the association observed due to shared method variance. However, sensitivity analyses showed that using the child as the reporter at the outcome did not change the overall results. Lastly, despite being multi-ethnic and diverse, the study sample available for analysis consisted of, for example, more individuals of European descent and more highly educated individuals when compared to the original sample at study enrollment.

CONCLUSIONS

Sports participation during early childhood was modestly associated with internalizing symptoms in adolescence. We did not observe associations between other types of physical activities and psychiatric symptoms at these ages. Among all neurobiological data, psychological constructs and behaviors examined, self-esteem was identified as the mediating factor through which sports relates to internalizing symptoms in youth. Further studies might explore whether larger effects are present in certain subgroups (e.g., children at high risk of developing psychiatric symptoms), different ages, or structured sport-based interventions.

ARTICLE INFORMATION

Authors affiliations: Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, the Netherlands (María Rodriguez-Ayllon, Amy Hofman, Trudy Voortman, Meike W. Vernooij); Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium (Alexander Neumann); VIB Center for Molecular Neurology, Antwerp, Belgium (Alexander Neumann); Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC University Medical Center Rotterdam, the Netherlands (Pauline W. Jansen, Ryan L. Muetzel); Department of Psychology, Education and Child Studies, Erasmus University Rotterdam, Rotterdam, the Netherlands (Pauline W. Jansen); Division of Human Nutrition and Health, Wageningen University & Research, the Netherlands (Trudy Voortman); Centre for Active Living and Learning, University of Newcastle, Australia (David R Lubans); Department of Public Health, Erasmus Medical Center, Rotterdam, Netherlands (Junwen Yang-Huang); Department of Radiology and Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands (Meike W. Vernooij).

Author Contributions: Dr. Ryan L. Muetzel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: María Rodriguez-Ayllon, Meike W. Vernooij, Ryan L. Muetzel.

Acquisition, analysis, or interpretation of data: María Rodriguez-Ayllon, Alexander Neumann, Pauline W. Jansen, Junwen Yang-Huang, Trudy Voortman, Meike W. Vernooij, Ryan L. Muetzel.

Drafting of the manuscript: María Rodriguez-Ayllon, Alexander Neumann, Amy Hofman, Pauline W. Jansen, Trudy Voortman, Junwen Yang-Huang, Hein Raat, David R Lubans, Meike W. Vernooij, Ryan L. Muetzel.

Critical revision of the manuscript for important intellectual content: David R Lubans.

Statistical analysis: María Rodriguez-Ayllon, Alexander Neumann, Ryan L. Muetzel.

Supervision: Meike W. Vernooij, Ryan L. Muetzel.

Conflict of Interest Disclosures: The authors report no biomedical financial interests or potential conflicts of interest.

Funding/Support: María Rodriguez-Ayllon was supported by the Ramon Areces and Alicia Koplowitz Foundations. This study was supported by the Sophia Foundation (S18-20) and Netherlands Organization for Health Research and Development (ZonMw). Supercomputing resources were supported by the Netherlands Organization for Scientific Research (Exacte Wetenschappen) and SURFsara (Snellius Compute Cluster, www.surfsara.nl). The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and the Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, and the Stichting Trombosedienst en Artsenlaboratorium Rijnmond. The general design of the Generation R Study was made possible by financial support from the Erasmus Medical Center, Rotterdam, ZonMw, the Netherlands Organization for Scientific Research, and the Ministry of Health, Welfare, and Sport. David Lubans is supported by a National Health and Medical Research Council Research Fellowship (APP1154507). The authors gratefully acknowledge the contributions of the participating children and parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Access to data and data analysis: María Rodriguez-Ayllon and Ryan L. Muetzel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Patel V, Flisher AJ, Hetrick S, McGorry P. Mental health of young people: a global public-health challenge. *Lancet*. 2007;369(9569):1302-1313. doi:10.1016/S0140-6736(07)60368-7
2. Rodriguez-Ayllon M, Estévez-López F, Cadenas-Sanchez C, et al. Physical activity, sedentary behaviour and mental health in young people: A review of reviews. In: *Adolescent Health and Wellbeing: Current Strategies and Future Trends*. Springer International Publishing; 2019:35-73. doi:10.1007/978-3-030-25816-0_3
3. Rodriguez-Ayllon M, Cadenas-Sánchez C, Estévez-López F, et al. Role of Physical Activity and Sedentary Behavior in the Mental Health of Preschoolers, Children and Adolescents: A Systematic Review and Meta-Analysis. *Sports Med*. 2019;49(9):1383-1410. doi:10.1007/s40279-019-01099-5
4. Chaput JP, Willumsen J, Bull F, et al. 2020 WHO guidelines on physical activity and sedentary behaviour for children and adolescents aged 5–17 years: summary of the evidence. *International Journal of Behavioral Nutrition and Physical Activity*. 2020;17(1):1-9. doi:10.1186/S12966-020-01037-Z/TABLES/6
5. Choi KW, Chen CY, Stein MB, et al. Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults: A 2-Sample Mendelian Randomization Study. *JAMA Psychiatry*. 2019;76(4):399-408. doi:10.1001/JAMAPSYCHIATRY.2018.4175
6. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54(24):1451-1462. doi:10.1136/bjsports-2020-102955
7. Lubans D, Richards J, Hillman C, et al. Physical Activity for Cognitive and Mental Health in Youth: A Systematic Review of Mechanisms. *Pediatrics*. 2016;138(3):e20161642-e20161642. doi:10.1542/peds.2016-1642
8. Stillman CM, Esteban-Cornejo I, Brown B, Bender CM, Erickson KI. Effects of Exercise on Brain and Cognition Across Age Groups and Health States. *Trends Neurosci*. 2020;43(7):533-543. doi:10.1016/j.tins.2020.04.010
9. Erickson KI, Hillman C, Stillman CM, et al. Physical Activity, Cognition, and Brain Outcomes: A Review of the 2018 Physical Activity Guidelines. *Med Sci Sports Exerc*. 2019;51(6):1242-1251. doi:10.1249/MSS.0000000000001936
10. Zhang FF, Peng W, Sweeney JA, Jia ZY, Gong QY. Brain structure alterations in depression: Psychoradiological evidence. *CNS Neurosci Ther*. 2018;24(11):994-1003. doi:10.1111/cns.12835
11. Valkenborghs SR, Hillman CH, Nilsson M, et al. Effect of high-intensity interval training on hippocampal metabolism in older adolescents. *Psychophysiology*. 2022;00:e14090. doi:10.1111/PSYP.14090
12. Rodriguez-Ayllon M, Derks IPM, van den Dries MA, et al. Associations of physical activity and screen time with white matter microstructure in children from the general population. *Neuroimage*. 2019;205:116258. doi:10.1016/j.neuroimage.2019.116258
13. Conley MI, Hindley I, Baskin-Sommers A, Gee DG, Casey BJ, Rosenberg MD. The importance of social factors in the association between physical activity and depression in children. *Child Adolesc Psychiatry Ment Health*. 2020;14(1):28. doi:10.1186/s13034-020-00335-5
14. Petty KH, Davis CL, Tkacz J, Young-Hyman D, Waller JL. Exercise Effects on Depressive Symptoms and Self-Worth in Overweight Children: A Randomized Controlled Trial*. *J Pediatr Psychol*. 2009;34(9):929. doi:10.1093/jpepsy/jsp007
15. Lang C, Brand S, Feldmeth AK, Holsboer-Trachsler E, Pühse U, Gerber M. Increased self-reported and objectively assessed physical activity predict sleep quality among adolescents. *Physiol Behav*. 2013;120:46-53. doi:10.1016/j.physbeh.2013.07.001
16. Gorham LS, Jernigan T, Hudziak J, Barch DM. Involvement in Sports, Hippocampal Volume, and Depressive Symptoms in Children. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2019;4(5):484-492. doi:10.1016/j.bpsc.2019.01.011

17. Cerin E. Ways of unraveling how and why physical activity influences mental health through statistical mediation analyses. *Ment Health Phys Act*. 2010;3(2):51-60. doi:10.1016/j.mhpa.2010.06.002
18. Jaddoe VW v., Mackenbach JP, Moll HA, et al. The Generation R Study: Design and cohort profile. *Eur J Epidemiol*. 2006;21(6):475-484. doi:10.1007/s10654-006-9022-0
19. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol*. 2016;31(12):1243-1264. doi:10.1007/s10654-016-0224-9
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344-349. doi:10.1016/j.jclinepi.2007.11.008
21. Achenback TM, Rescorla L a. Manual for the ASEBA School-Age Forms and Profiles. *Manual for the ASEBA School -Age Forms & Profiles*. Published online 2003:99-107.
22. Ivanova MY, Achenbach TM, Rescorla LA, et al. Preschool psychopathology reported by parents in 23 societies: Testing the seven-syndrome model of the child behavior checklist for ages 1.55. *J Am Acad Child Adolesc Psychiatry*. 2010;49(12):1215-1224. doi:10.1016/j.jaac.2010.08.019
23. White T, Muetzel RL, el Marroun H, et al. Paediatric population neuroimaging and the Generation R Study: the second wave. *Eur J Epidemiol*. 2018;33(1):99-125. doi:10.1007/s10654-017-0319-y
24. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. NeuroImage. 2012;62:782-790. doi:10.1016/j.neuroimage.2011.09.015
25. López-Vicente M, Agcaoglu O, Pérez-Crespo L, et al. Developmental Changes in Dynamic Functional Connectivity From Childhood Into Adolescence. *Front Syst Neurosci*. 2021;15. doi:10.3389/FNSYS.2021.724805/FULL
26. Harter S. Manual for the self-perception profile for children. *Department of Psychology*. Published online 1985.
27. Truby H, Paxton SJ. Development of the Children's Body Image Scale. *British Journal of Clinical Psychology*. 2002;41(2):185-203. doi:10.1348/014466502163967
28. Parker JG, Asher SR. Friendship and friendship quality in middle childhood: Links with peer group acceptance and feelings of loneliness and social dissatisfaction. *Dev Psychol*. 1993;29(4):611-621. doi:10.1037/0012-1649.29.4.611
29. de Lijster JM, van den Dries MA, van der Ende J, et al. Developmental Trajectories of Anxiety and Depression Symptoms from Early to Middle Childhood: a Population-Based Cohort Study in the Netherlands. *J Abnorm Child Psychol*. 2019;47(11):1785-1798. doi:10.1007/S10802-019-00550-5/TABLES/4
30. Bruni O, Ottaviano S, Guidetti V, et al. The Sleep Disturbance Scale for Children (SDSC) Construct ion and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J Sleep Res*. 1996;5(4):251-261. doi:10.1111/J.1365-2869.1996.00251.X
31. Koopman-Verhoeff ME, Serdarevic F, Kocevska D, et al. Preschool family irregularity and the development of sleep problems in childhood: a longitudinal study. *J Child Psychol Psychiatry*. 2019;60(8):857-865. doi:10.1111/JCPP.13060
32. van der Velde LA, Nguyen AN, Schoufour JD, et al. Diet quality in childhood: the Generation R Study. *Eur J Nutr*. 2019;58(3):1259. doi:10.1007/S00394-018-1651-Z
33. Fredriks AM, van Buuren S, Burgmeijer RJ, et al. Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr Res*. 2000;47(3):316-323. Accessed April 4, 2018. http://www.ncbi.nlm.nih.gov/pubmed/10709729
34. Tellegen, Winkel, Wijnberg-Williams, Laros. *Snijders-Oomen Niet-Verbale Intelligentietest: SON-R 2-1/2 -to-7*. Boom Testu.; 2005. Accessed January 29, 2019. https://www.worldcat.org/title/son-r-212-7-snijders-oomen-niet-verbale-intelligentietest-handleiding-en-verantwoording/oclc/66564516/editions?referer=di&editionsView=true
35. R: The R Project for Statistical Computing. Accessed July 21, 2020. https://www.r-project.org/

36. Benjamini Y, Hochberg Y. *Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing*.; 1995. Accessed January 28, 2019. https://www.jstor.org/stable/2346101?seq=1#metadata_info_tab_contents
37. Rosseel Y. Lavaan: An R package for structural equation modeling. *J Stat Softw*. 2012;48(1):1-36. doi:10.18637/jss.v048.i02
38. Carter T, Morres ID, Meade O, Callaghan P. The Effect of Exercise on Depressive Symptoms in Adolescents: A Systematic Review and Meta-Analysis. *J Am Acad Child Adolesc Psychiatry*. 2016;55(7):580-590. doi:10.1016/J.JAAC.2016.04.016
39. Larun L, Nordheim L v., Ekeland E, Hagen KB, Heian F. Exercise in prevention and treatment of anxiety and depression among children and young people. *Cochrane Database of Systematic Reviews*. 2006;(3). doi:10.1002/14651858.CD004691.PUB2/MEDIA/CDSR/CD004691/IMAGE_N/NCD004691-CMP-008-04.PNG
40. Brown HE, Pearson N, Braithwaite RE, Brown WJ, Biddle SJH. Physical activity interventions and depression in children and adolescents: A systematic review and meta-analysis. *Sports Medicine*. 2013;43(3):195-206. doi:10.1007/S40279-012-0015-8/TABLES/4
41. Brunet J, Sabiston CM, Chaiton M, et al. The association between past and current physical activity and depressive symptoms in young adults: A 10-year prospective study. *Ann Epidemiol*. 2013;23(1):25-30. doi:10.1016/j.annepidem.2012.10.006
42. Sonstroem RJ, Morgan WP. Exercise and self-esteem: rationale and model. *Med Sci Sports Exerc*. 1989;21(3):329-337. Accessed October 29, 2018. http://www.ncbi.nlm.nih.gov/pubmed/2659918
43. Feldman AF, Matjasko JL. The Role of School-Based Extracurricular Activities in Adolescent Development: A Comprehensive Review and Future Directions: *http://dx.doi.org/103102/00346543075002159*. 2016;75(2):159-210. doi:10.3102/00346543075002159
44. Nguyen Ho PT, Ha Pham Bich T, Tong T, et al. Mechanisms linking physical activity with psychiatric symptoms across the lifespan: A systematic review. *medRxiv. doi: https://doi.org/10.1101/2022.07.13.22277479*
45. Kipp LE, Weiss MR. Physical activity and self-perceptions among children and adolescents. Published online 2013:187-199. Accessed September 24, 2018. https://experts.umn.edu/en/publications/physical-activity-and-self-perceptions-among-children-and-adolesc
46. Lubans DR, Lonsdale C, Cohen K, et al. Framework for the design and delivery of organized physical activity sessions for children and adolescents: Rationale and description of the "SAAFE" teaching principles. *International Journal of Behavioral Nutrition and Physical Activity*. 2017;14(1). doi:10.1186/s12966-017-0479-x
47. Hulteen RM, Smith JJ, Morgan PJ, et al. Global participation in sport and leisure-time physical activities: A systematic review and meta-analysis. *Prev Med (Baltim)*. 2017;95:14-25. doi:10.1016/J.YPMED.2016.11.027
48. Rijlaarsdam J, Stevens GWJM, van der Ende J, et al. Economic disadvantage and young children's emotional and behavioral problems: mechanisms of risk. *J Abnorm Child Psychol*. 2013;41(1):125-137. doi:10.1007/S10802-012-9655-2
49. Appleton AA, Buka SL, McCormick MC, Koenen KC, Loucks EB, Kubzansky LD. The Association Between Childhood Emotional Functioning and Adulthood Inflammation Is Modified by Early-Life Socioeconomic Status. *Health Psychol*. 2012;31(4):413-422. doi:10.1037/A0027300
50. Zinn ME, Huntley ED, Keating DP. Resilience in Adolescence: Prospective Self Moderates the Association of Early Life Adversity with Externalizing Behavior Problems. *J Adolesc*. 2020;81:61. doi:10.1016/J.ADOLESCENCE.2020.04.004
51. Kim Y, Lee H, Park A. Patterns of adverse childhood experiences and depressive symptoms: self-esteem as a mediating mechanism. *Soc Psychiatry Psychiatr Epidemiol*. 2022;57(2):331-341. doi:10.1007/S00127-021-02129-2/FIGURES/2

52. Afifi TO, MacMillan HL. Resilience following child maltreatment: a review of protective factors. *Can J Psychiatry*. 2011;56(5):266-272. doi:10.1177/070674371105600505
53. Bruner MW, McLaren CD, Sutcliffe JT, et al. The effect of sport-based interventions on positive youth development: a systematic review and meta-analysis. *https://doi.org/101080/1750984X20211875496*. Published online 2021. doi:10.1080/1750984X.2021.1875496
54. Rodriguez-Ayllon M, Plaza-Florido A, Mendez-Gutierrez A, et al. The effects of a 20-week exercise program on blood-circulating biomarkers related to brain health in children with overweight or obesity: The ActiveBrains project. *medRxiv*. doi:10.1101/2022.07.28.22278146
55. Frenkel D, Wilkinson K, Zhao L, et al. Scara1 deficiency impairs clearance of soluble amyloid-β by mononuclear phagocytes and accelerates Alzheimer's-like disease progression. *Nat Commun*. 2013;4. doi:10.1038/ncomms3030
56. Ortega FB, Mora-Gonzalez J, Cadenas-Sanchez C, et al. Effects of exercise on brain health outcomes in children with overweight/obesity: the ActiveBrains randomized controlled trial. *JAMA Netw Open*. 2022; 1;5(8):e2227893. doi: 10.1001/jamanetworkopen.2022.27893. PMID: 36040742; PMCID: PMC9428743.

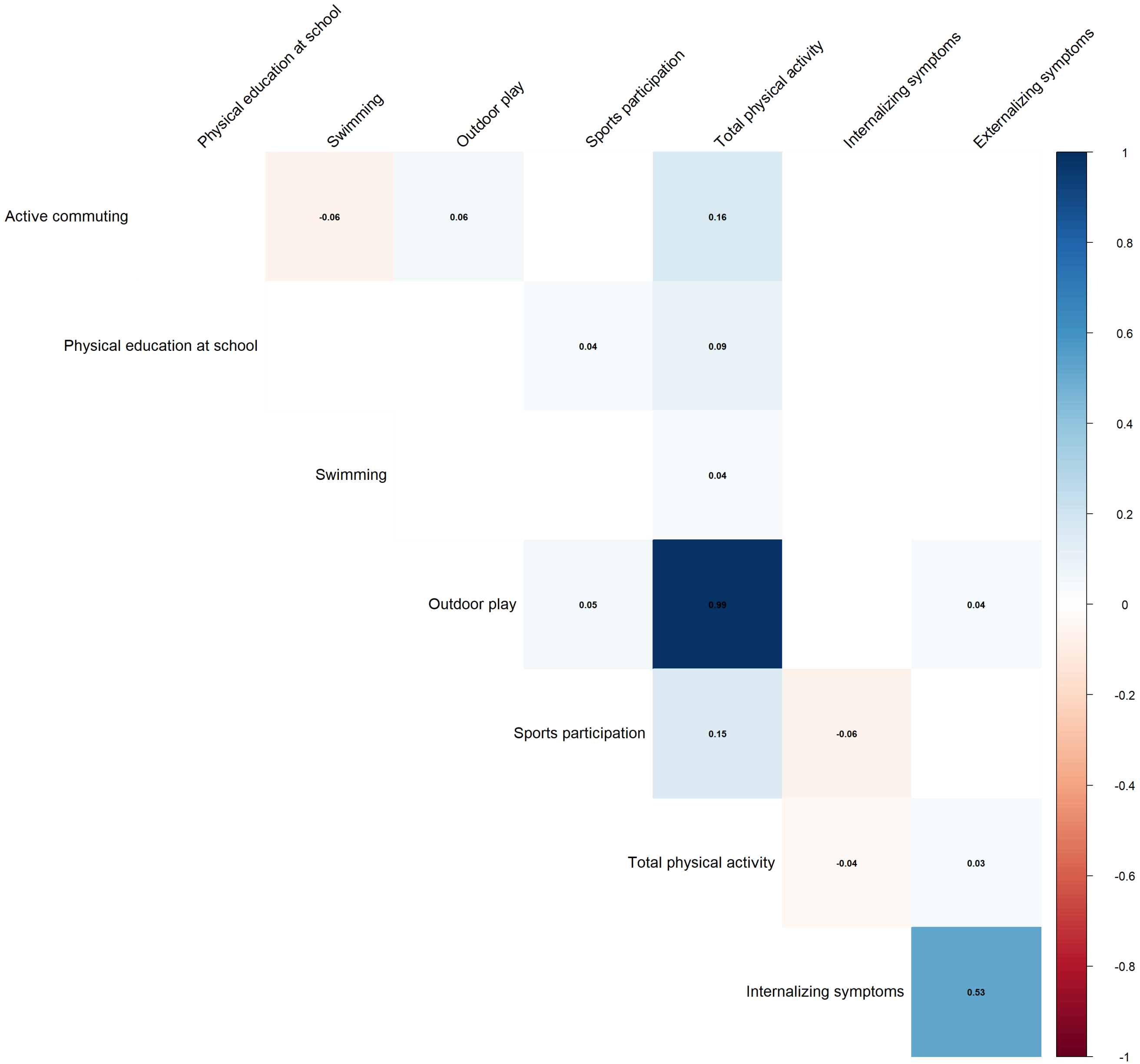
Table 1. Sample characteristics (n=4,216)

	Mean/%	SD
Child characteristics		
Sex		
Girls,%	50.2	
Age at 6 assessment, years (visit 1)	6.0	0.4
Age at 10 assessment, years (visit 2)	9.8	0.3
Age at 13 assessment, years (visit 3)	13.5	0.4
Body mass index, kg/m^2	16.0	1.6
Behavior problems, sum score (CBCL)	18.7	15.3
Non-verbal IQ	103.4	14.6
Parental characteristics		
Maternal education,%		
Higher education,%	63.4	
Lower education, %	36.6	
Parental National Origin		
Dutch,%	68.0	
Other than Dutch,%	32.0	

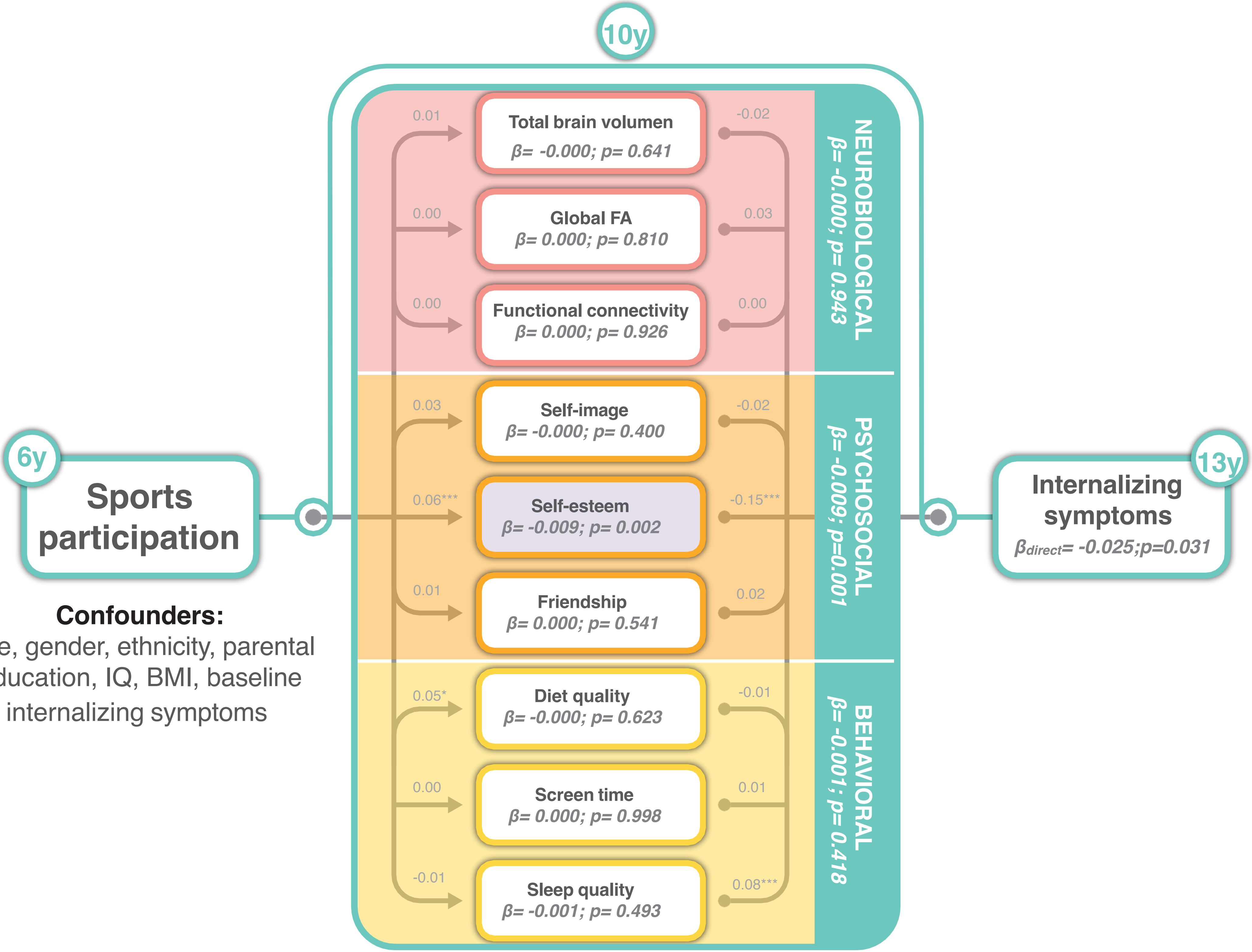
*Note: CBCL= Child Behavior Checklist school-age, IQ= intelligence quotient. Maternal education level was defined by the highest completed education and divided into 2 categories ranging from low (from no education to high school) to high education level (from higher vocational education to university). Characteristics of the study sample are presented as means and standard deviations (SD). Of these, sex, parental education, and ethnicity were presented as a percentage.

Figure 1. Correlation between predictors and outcomes. Only significant correlation values before adjusting for multiple testing are colored ($p<0.05$). Corr= correlation coefficient based on Pearson´s method.

Figure 2. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in young people (n=4216). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old). β_{direct} = direct effect. β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * $p <0.05$, ** $p<0.01$, *** $p<0.001$.



Physical education at school
Swimming
Outdoor play
Sports participation
Total physical activity
Internalizing symptoms
Externalizing symptoms
Active commuting
-0.06
0.06
0.16
Physical education at school
0.04
0.09
Swimming
0.04
Outdoor play
0.05
0.99
0.04
Sports participation
0.15
-0.06
Total physical activity
-0.04
0.03
Internalizing symptoms
0.53
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1



Confounders:
Age, gender, ethnicity, parental education, IQ, BMI, baseline internalizing symptoms

Supplementary Online Content

Supplementary Material 1. STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Supplementary Material 2. Methods section

Study variables

Neurobiological mediators

High-resolution structural magnetic resonance imaging (MRI), diffusion weighted white matter imaging (DTI), and resting-state functional MRI were collected within a standardized protocol[1]. Briefly, MRI data were acquired with a 3Tesla GE MR-750W system (General Electric, Milwaukee, WI). Structural MRI data were processed through the FreeSurfer analysis suite, version 6.0 [1], which yielded anatomical labels for broad tissue classes (e.g., white and gray matter) and several brain structures (e.g., hippocampus and amygdala). Diffusion image preprocessing was conducted using the FMRIB Software Library (FSL), version 5.0.9[2]. The full procedure is described previously[3]. Briefly, probabilistic tractography was run on each subject's diffusion data using the fully automated FSL plugin AutoPtx[4]. Two metrics of white matter microstructure (i.e., fractional anisotropy [FA] and mean diffusivity [MD]), were derived globally (e.g., across multiple tracts) and for corpus callosum fibers (the forceps major and minor).

Dynamic functional network connectivity was estimated using the Group ICA Of fMRI Toolbox (GIFT) software1 (GroupICAT v4.0b)[5]. The full procedure has been described elsewhere[6] Briefly, we estimated that children occupied in general 1 of 5 connectivity configurations (states) during the measurement period. We used the number of transitions between these 5 states as global measure of dynamic functional network connectivity [for a more detailed explanation, see Rashid et al.[7]] in this study.

Psychosocial mediators

Children´s self-esteem was measured with an adapted 18-item question format of the Harter's Self Perception Profile for Children[8,9]. Five subscales were used: school competence, social acceptance, athletic competence, physical appearance, and behavioral conduct. All answers were added up to a final self-esteem score (range 18–54 points) with the highest score indicating the highest self-esteem. Missing values were replaced by the mean score of the remaining answers for the particular subscale[9]. If there were more than 30 percent of the answers missing per subscale the self-esteem score was coded as a missing value[9]. Because younger children were studied, the question format, as Wichstrom suggested, was applied to the validated self-perception profile for children (CBSK in Dutch)[10]. Details of the adaptation of the scale have been described elsewhere[9].

Body image was evaluated using the Children's Body Image Scale[11,12]. In brief, children's satisfaction with their body size was assessed using the same figures of the Children's Body Image Scale but including only the question "Which body would you like to have?" Body size satisfaction was defined as the difference between the categorical ratings of "ideal" body size and self-perception, with scores ranging from -6 to 6. A score of zero corresponded with the child being content with his/her body size category, a positive score was categorized as a desire to be thinner, and a negative score was defined as a desire to be heavier. We ended up with two categories: (1) satisfied and (2) unsatisfied (including wants to be fatter and wants to be thinner). The test-retest reliability of the Children´s Body Image Scale was previously supported[13].

Friendships were evaluated using an adapted version of the Friendship Quality Questionnaire (FQQ; Parker and Asher 1993)[14,15]. In total, 10 items of the original 40-item FQQ were selected based on expert opinion and relevance to the Dutch elementary school setting. Items represented subscales 'validation and caring' (i.e. we give each other compliments), 'companionship' (i.e. we are always together during our break at school), 'conflict resolution' (i.e. if we are angry at each other, we always talk it out), 'intimate exchange' (i.e. we tell each other secrets), and 'help and guidance' (if we need to get something done, we will help each other). Children rated how true each statement was about their best friend (1 = not true, 2=somewhat true, 3=very true, total range 10–30). Missing values were replaced by the mean score of the remaining items (weighted total score). If there were more than 20% of the answers missing, this was coded as a missing value.

This questionnaire has been validated using socio-metric rating methods and is predictive of both peer acceptance and feelings of loneliness[14].

Behavioral Mediators

Sleep quality was evaluated using six questions of the Sleep Disturbance Scale for Children[16,17]. Specifically, children completed six questions about perceived sleep, for example, 'Do you find it difficult to fall asleep?'; 'If you wake up at night, do you find it difficult to fall asleep again?';

‘Do you feel rested when you wake in the morning?’ (previously described in Koopman-Verhoeff et al., 2019[17]). Responses were scored on a three-point Likert scale (‘No’, ‘Sometimes’, or ‘Yes’; $\alpha = .64$). Items were summed; higher scores indicate lower sleep quality.

Overall, this tool is valid and reliable in evaluating the sleep disturbances of school-age children in clinical and non-clinical populations[16].

Diet quality was quantified by a predefined food-based diet quality score, based on Dutch dietary recommendations for 8-year-old children[18]. The detailed information is reported elsewhere[19]. In brief, diet quality score consisted of 10 components, including fruit (≥150 g/d); vegetables (≥150 g/d); whole grains (≥90 g/d); fish (≥60g/w); legumes (≥84g/w); nuts (≥15 g/d); dairy (≥300 g/d); oils and soft or liquid margarines (≥30 g/d); sugar-containing beverages (≤150 g/d); and high-fat and processed meat (≤250g/w). For each component, the ratio of reported and recommended intake was calculated[19,20]. Scores of the individual components were summed, resulting in a total score ranging from 0 to 10 on a continuous scale, with higher scores reflecting better adherence to the dietary guidelines.

The diet quality score was validated for intake of several macronutrients and micronutrients within children participating in the Generation R Study[19].

Lastly, information on the level of recreational screen time were obtained through a parent-reported questionnaire administered when children were 10 years old[21,22]. Overall, respondents were asked to indicate the number of days and hours per day their child: (i) watches television (including videos/DVDs) and (ii) uses a (game)computer or similar device (including video games). Recreational screen times were assessed separately for weekdays and weekend days but were combined to estimate the total hours per week spent in each activity. A total weekly recreational screen time score was calculated by adding the hours of playing video games and watching television.

Statistical analyses

Supplemental analyses

Regional MRI metrics selected based on previous evidence (i.e., hippocampal volume and fractional anisotropy (FA) and mean diffusivity (MD) in the corpus callosum)[23,24] instead of global measures (i.e., total brain volume, and global FA and MD) were included in the model. Furthermore, we explored the mechanisms linking physical activity with syndrome scale subdomains of internalizing symptoms (i.e., depression, anxiety, somatic symptoms) and externalizing symptoms (i.e., conduct problems, rule-breaking behavior, attention-deficit/hyperactivity problems). Lastly, Global MD instead of Global FA was included in the model.

Sensitivity analyses

We performed complete case analyses (participants with complete exposures, mediators, and outcomes data, n=1,025) to examine the impact of different missing handling approaches. Additionally, other sensitivity analyses were tested to evaluate the robustness of the findings. First, repeating the analyses in a sample of 3,921 participants after one of each sibling pairs was randomly excluded. Second, we ran our analyses without adjusting for psychiatry symptoms at the baseline. Third, we ran our analyses using the Child Behavior Checklist (CBCL) filled out by the children and the average measure of child and caregiver reports to avoid any overestimation due to shared method variance. Lastly, we explored the individual role of each mediator in the relationship between sports participation and internalizing symptoms to avoid multicollinearity between associated mediators (e.g., self-image and physical appearance subdomain of overall self-esteem).

Supplementary Material 3. Results Section

Supplemental analyses

The mediation model including regional MRI measures, selected based on previous evidence (i.e., hippocampal volume and FA and MD in the corpus callosum), instead of global measures (i.e., total brain volume, and global FA and MD) is presented in **Figure S6**. Similarly, only self-esteem mediated the association of sports participation with internalizing symptoms (β=-0.009, standard error (SE)= 0.016, p=0.002). Analyses performed to explore whether sports participation was associated with the subdomains of internalizing symptoms (i.e., depression, anxiety, somatic symptoms) are presented separately in **Figure S7**, **Figure S8,** and **Figure S9**, respectively. Similarly, only self-esteem mediated the association between sports participation and the different subdomains of internalizing symptoms (β ranged from -0.005 to -0.009; all p<0.008). Lastly, results were similar when global MD instead of global FA was included in the model.

Sensitivity analyses

Overall, results were comparable when the sample was reduced to those with complete data (n=1,025, **Figure S10**), when siblings were excluded (n=3,921, **Figure S11**), when we did not adjust for internalizing symptoms at baseline (**Figure S12**), when children self-reports instead of primary caregivers report were included in the model (n=4,060, **Figure S13**), and when mediators were included individually in the model (**Figure S14**). Specifically, self-esteem mediated the relationship between sports participation and internalizing symptoms (β ranged from -0.009 to -0.014; all p<0.022).

REFERENCES

1. White T, Muetzel RL, el Marroun H, et al. Paediatric population neuroimaging and the Generation R Study: the second wave. *Eur J Epidemiol*. 2018;33(1):99-125. doi:10.1007/s10654-017-0319-y
2. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. NeuroImage. 2012;62:782-790. doi:10.1016/j.neuroimage.2011.09.015
3. Muetzel RL, Blanken LME, van der Ende J, et al. Tracking Brain Development and Dimensional Psychiatric Symptoms in Children: A Longitudinal Population-Based Neuroimaging Study. *American Journal of Psychiatry*. Published online August 18, 2017:appi.ajp.2017.1. doi:10.1176/appi.ajp.2017.16070813
4. de Groot M, Ikram MA, Akoudad S, et al. Tract-specific white matter degeneration in aging: The Rotterdam Study. *Alzheimer's and Dementia*. 2015;11(3):321-330. doi:10.1016/j.jalz.2014.06.011
5. Calhoun VD, Adali T, Pearlson GD, Pekar JJ. A method for making group inferences from functional MRI data using independent component analysis. *Hum Brain Mapp*. 2001;14(3):140. doi:10.1002/HBM.1048
6. López-Vicente M, Agcaoglu O, Pérez-Crespo L, et al. Developmental Changes in Dynamic Functional Connectivity From Childhood Into Adolescence. *Front Syst Neurosci*. 2021;15. doi:10.3389/FNSYS.2021.724805/FULL
7. Rashid B, Blanken LME, Muetzel RL, et al. Connectivity dynamics in typical development and its relationship to autistic traits and autism spectrum disorder. *Hum Brain Mapp*. 2018;39(8):3127. doi:10.1002/HBM.24064
8. Harter S. Manual for the self-perception profile for children. *Department of Psychology*. Published online 1985.
9. Kragt L, Wolvius EB, Jaddoe VWV, Tiemeier H, Ongkosuwito EM. Influence of self-esteem on perceived orthodontic treatment need and oral health-related quality of life in children: the Generation R Study. *Eur J Orthod*. 2018;40(3):254-261. doi:10.1093/EJO/CJX054
10. Maciej Serda, Becker FG, Cleary M, et al. Handleiding Competentiebelevingsschaal voor Kinderen (CBSK). G. Balint, Antala B, Carty C, Mabieme JMA, Amar IB, Kaplanova A, eds. *Uniwersytet śląski*. 1997;7(1):343-354. doi:10.2/JQUERY.MIN.JS
11. Truby H, Paxton SJ. Development of the Children's Body Image Scale. *British Journal of Clinical Psychology*. 2002;41(2):185-203. doi:10.1348/014466502163967
12. Leppers I, Tiemeier H, Swanson SA, et al. Agreement between Weight Status and Perceived Body Size and the Association with Body Size Satisfaction in Children. *Obesity (Silver Spring)*. 2017;25(11):1956-1964. doi:10.1002/OBY.21934
13. Truby H, Paxton SJ. The Children's Body Image Scale: Reliability and use with international standards for body mass index. *British Journal of Clinical Psychology*. 2008;47(1):119-124. doi:10.1348/014466507X251261
14. Parker JG, Asher SR. Friendship and friendship quality in middle childhood: Links with peer group acceptance and feelings of loneliness and social dissatisfaction. *Dev Psychol*. 1993;29(4):611-621. doi:10.1037/0012-1649.29.4.611
15. de Lijster JM, van den Dries MA, van der Ende J, et al. Developmental Trajectories of Anxiety and Depression Symptoms from Early to Middle Childhood: a Population-Based Cohort Study in the Netherlands. *J Abnorm Child Psychol*. 2019;47(11):1785-1798. doi:10.1007/S10802-019-00550-5/TABLES/4
16. Bruni O, Ottaviano S, Guidetti V, et al. The Sleep Disturbance Scale for Children (SDSC) Construct ion and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J Sleep Res*. 1996;5(4):251-261. doi:10.1111/J.1365-2869.1996.00251.X
17. Koopman-Verhoeff ME, Serdarevic F, Kocevska D, et al. Preschool family irregularity and the development of sleep problems in childhood: a longitudinal study. *J Child Psychol Psychiatry*. 2019;60(8):857-865. doi:10.1111/JCPP.13060

18. The Wheel of Five is the practical information tool used by the Netherlands Nutrition Centre to.
19. van der Velde LA, Nguyen AN, Schoufour JD, et al. Diet quality in childhood: the Generation R Study. *Eur J Nutr*. 2019;58(3):1259. doi:10.1007/S00394-018-1651-Z
20. Mou Y, Jansen PW, Raat H, Nguyen AN, Voortman T. Associations of family feeding and mealtime practices with children's overall diet quality: Results from a prospective population-based cohort. *Appetite*. 2021;160. doi:10.1016/J.APPET.2020.105083
21. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol*. 2016;31(12):1243-1264. doi:10.1007/s10654-016-0224-9
22. Rodriguez-Ayllon M, Derks IPM, van den Dries MA, et al. Associations of physical activity and screen time with white matter microstructure in children from the general population. *Neuroimage*. 2020;205:116258. doi:10.1016/j.neuroimage.2019.116258
23. Zhang FF, Peng W, Sweeney JA, Jia ZY, Gong QY. Brain structure alterations in depression: Psychoradiological evidence. *CNS Neurosci Ther*. 2018;24(11):994-1003. doi:10.1111/cns.12835
24. Chaddock-Heyman L, Erickson KI, Kienzler C, et al. Physical Activity Increases White Matter Microstructure in Children. *Front Neurosci*. 2018;12:950. doi:10.3389/FNINS.2018.00950

Table S1. Sample characteristics of participants with complete cases in predictors, outcomes, and mediators (n=1,025)

	Mean/%	SD
Child characteristics		
Sex		
Girls,%	50.8	
Age at 6 assessment, years (visit 1)	5.9	0.2
Age at 10 assessment, years (visit 2)	9.8	0.3
Age at 13 assessment, years (visit 3)	13.4	0.2
Body mass index, kg/m^2	15.8	1.3
Behavior problems, sum score (CBCL)	17.2	13.9
Non-verbal IQ	106.2	14.6
Parental characteristics		
Maternal education,%		
Higher education,%	72.5	
Lower education, %	27.5	
Parental National Origin		
Dutch,%	76.0	
Other than Dutch,%	24.0	

CBCL= Child Behavior Checklist school-age, IQ= intelligence quotient. Maternal education level was defined by the highest completed education and divided into two categories ranging from low (from no education to high school) to high education level (from higher vocational education to university). Characteristics of the study sample are presented as means and standard deviations (SD). Of these, sex, parental education, and ethnicity were presented as a percentage.

Table S2. Exposures, mediators, and outcomes characteristics.

	Mean/%	SD
Exposures at 6 (h/w)		
Total physical activity	14.62	8.08
Active commuting	0.87	0.88
Outdoor play	11.23	7.91
Sports participation	0.56	0.84
Swimming	0.69	0.43
Physical education at school	1.24	0.60
Mediators at 10		
Neurobiological		
Total brain volume, cm^3*	7.67	0.63
Global FA	0.44	0.02
Global MD#	0.01	0.00
Number of transitions	8.18	2.87
Psychosocial		
Self-image		
Satisfied, %	63.9	
Self-esteem (18–54)	45.67	4.28
Friendship (10-30)	24.03	3.27
Behavioral		
Sleep (6-18)	10.92	2.46
Screen time (h/w)	16.37	10.55
Diet quality (0-10)	4.55	1.22
Outcomes at 13		
Overall CBCL score	18.09	16.11
Internalizing symptoms	5.50	5.70
Externalizing symptoms	4.15	5.17

h/w= hours per week, FA= fractional anisotropy, MD=mean diffusivity, CBCL= the Child Behavior Checklist.*values are x 10^5. #values are multiplied by 10000000.

Table S3. Included-excluded comparison sample characteristics.

	Participants at birth (n=9,901)		Participants at age 6 (n=6690)		Participants with complete cases in the predictor at age 6 and the outcome at age 13 (n= n=4,216)	
	Mean/%	SD	Mean/%	SD	Mean/%	SD
Child characteristics						
Sex						
Girls,%	49.3		49.9		50.2	
Body mass index, kg/m^2			16.2	1.9	16.0	1.6
Behavior problems, sum score (CBCL)			19.9	16.6	18.7	15.3
Non-verbal IQ			100.7	15.2	103.4	14.6
Parental characteristics						
Maternal education,%						
Higher education,%	42.1		45.6		57.2	
Lower education, %	57.9		54.4		42.8	
Parental National Origin						
Dutch,%	53.7		56.9		68.0	
Other than Dutch,%	46.3		48.5		32.0	

CBCL= Child Behavior Checklist school-age, IQ= intelligence quotient. Maternal education level was defined by the highest completed education and divided into two categories ranging from low (from no education to high school) to high education level (from higher vocational education to university). For the comparison of our results in this table, we used maternal education at birth. In the main analyses, we used maternal education at 6 for being closer to our predictor variable. Characteristics of the study sample are presented as means and standard deviations (SD). Of these, sex, parental education, and ethnicity were presented as a percentage.

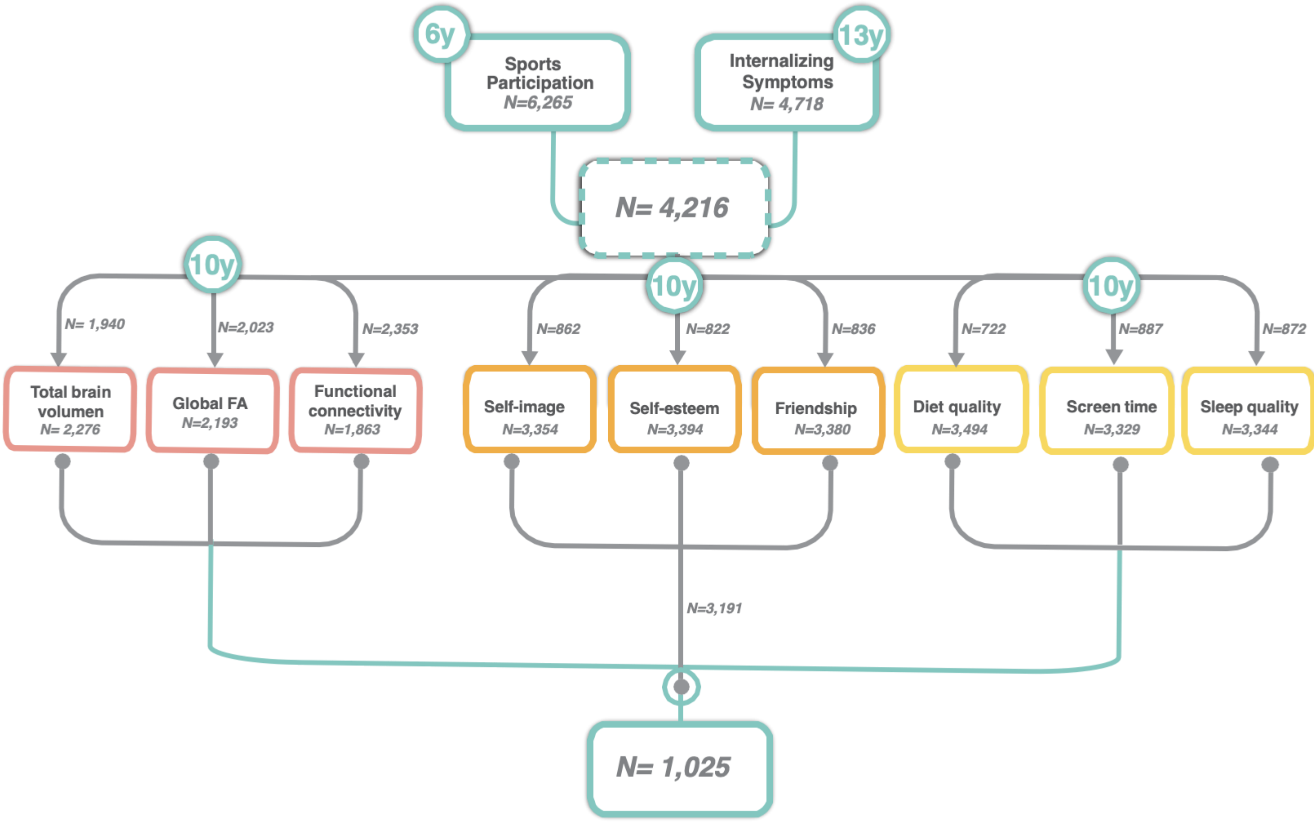


Figure S1. Flow chart. Box with dotted lines indicate the sample used in the main analysis. y=years old.

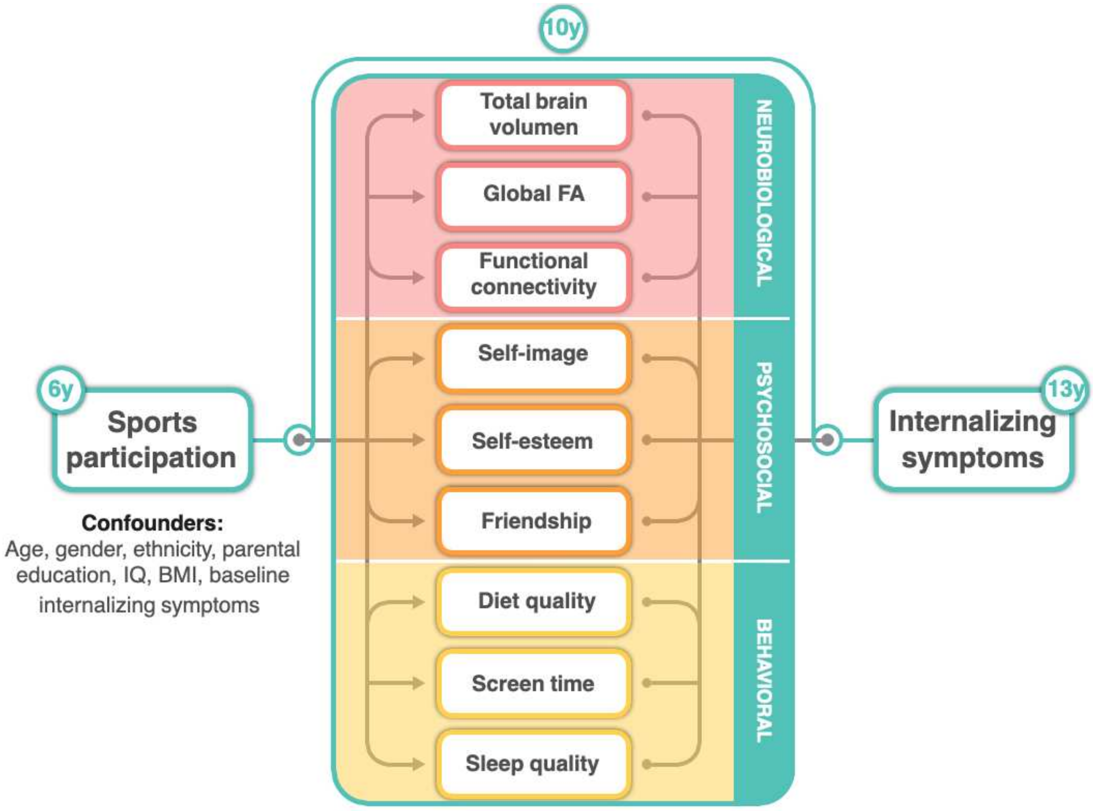


Figure S2. Visualization of the mediation modeling approach. BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old.

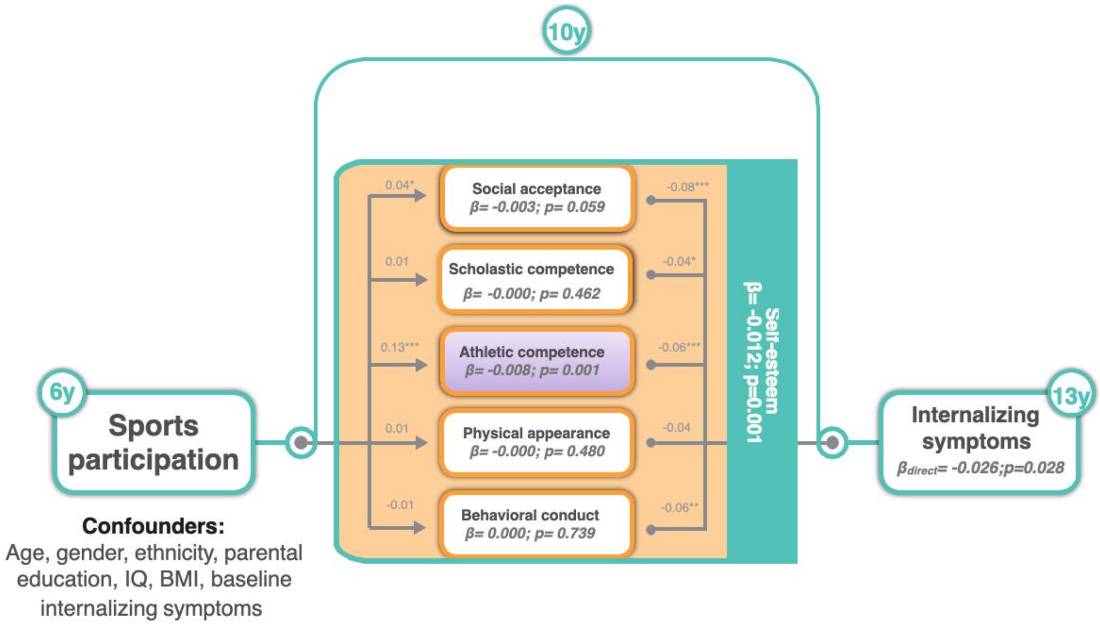


Figure S3. Integrative mediation model to explore the mediating role of self-esteem domains in the relationship between sports participation and internalizing symptoms in young people (n=4,216): a posteriori analysis. BMI=body mass index; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

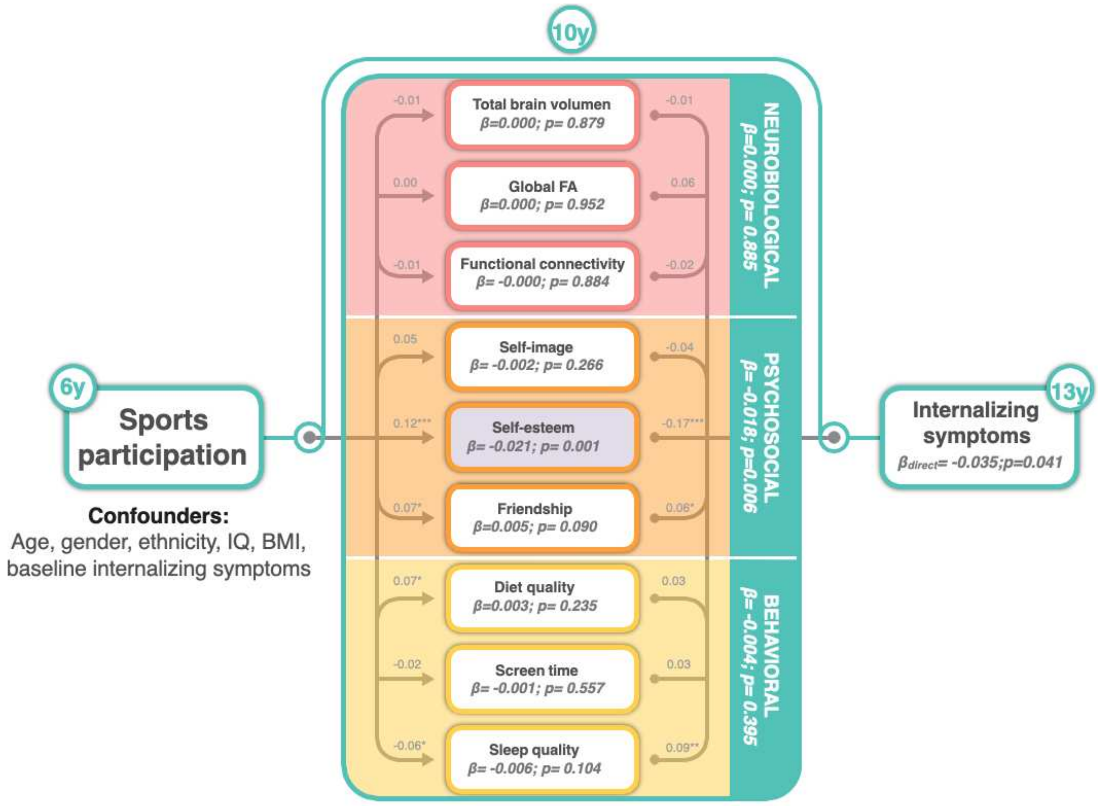


Figure S4. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in children who caregivers have a low educational status (n=1,543). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

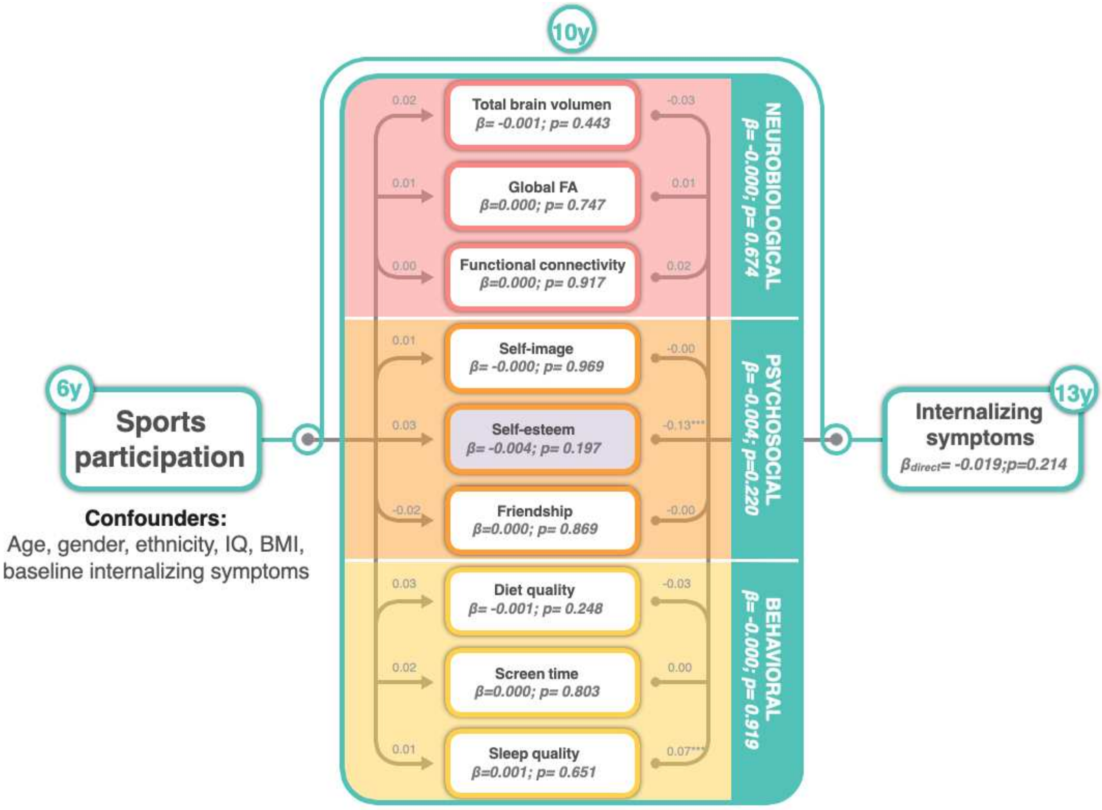


Figure S5. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in children who caregivers have a high educational status (n=2,670). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

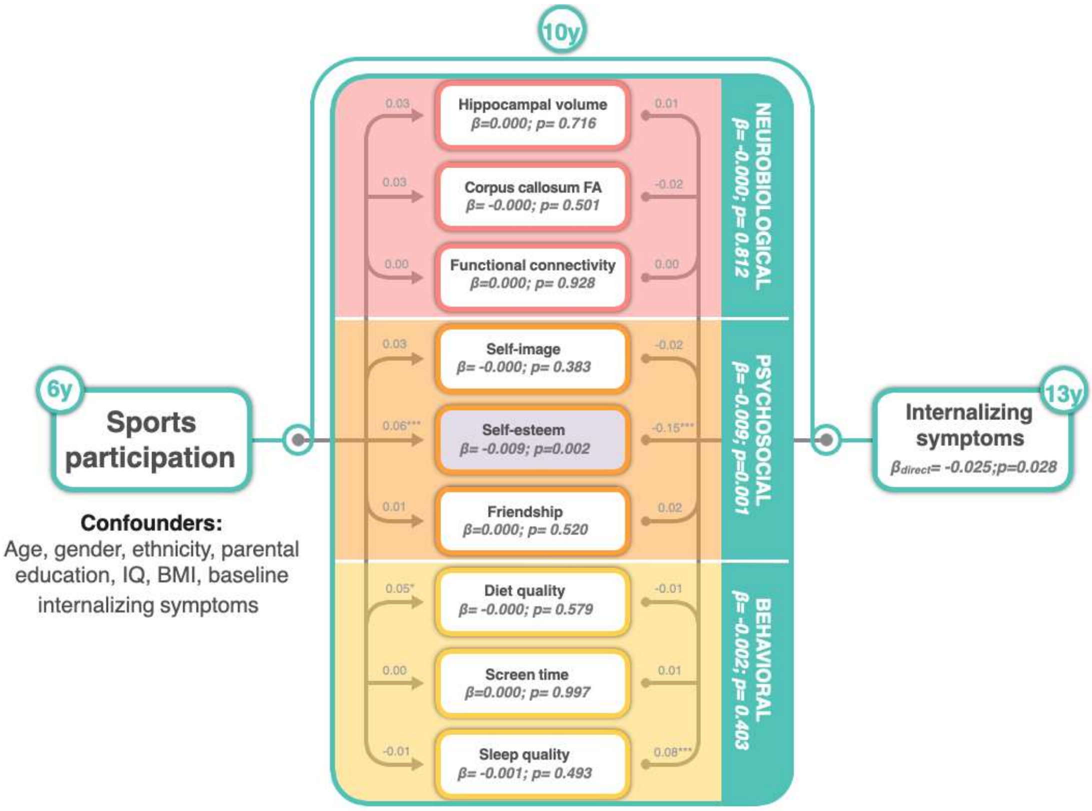


Figure S6. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in young people (n=4,216) including hippocampal volume and corpus callosum fractional anisotropy instead of global measures. BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

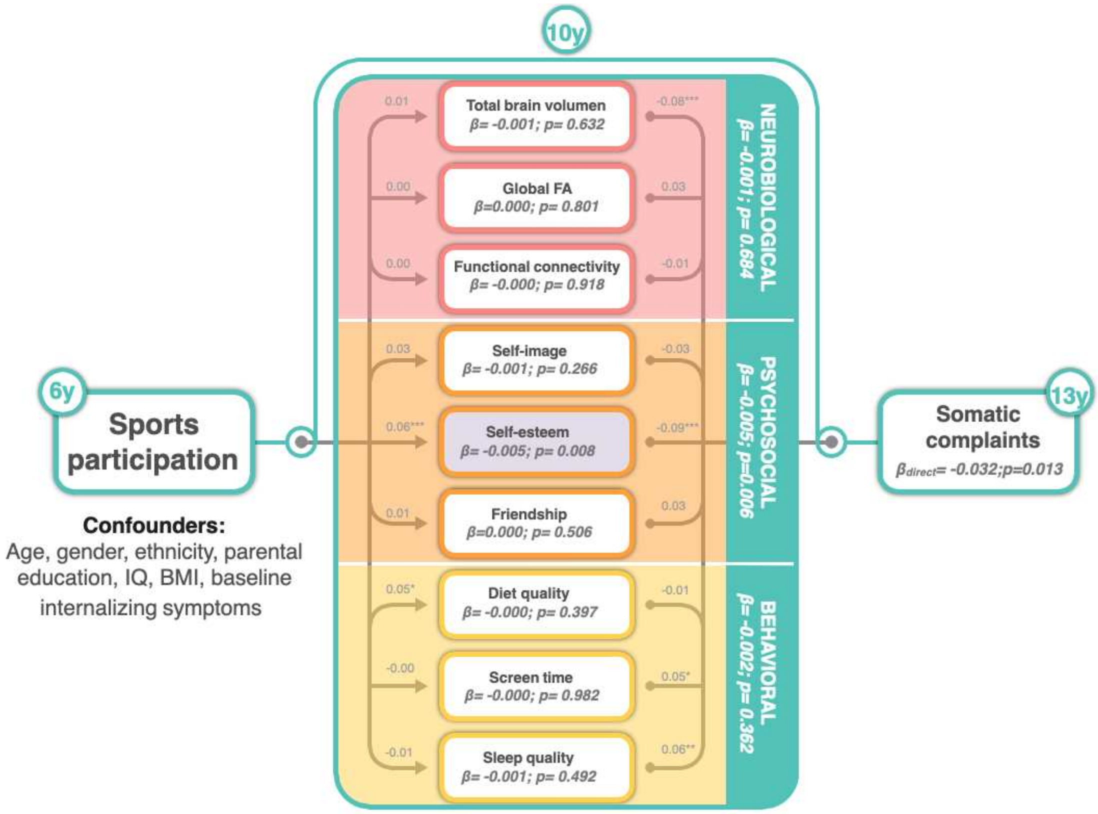


Figure S7. Integrative mediation model on the mechanisms linking sports participation and somatic complaints in young people (n=4,216). BMI=body mass index; IQ= intelligence quotient; MD= mean diffusivity; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

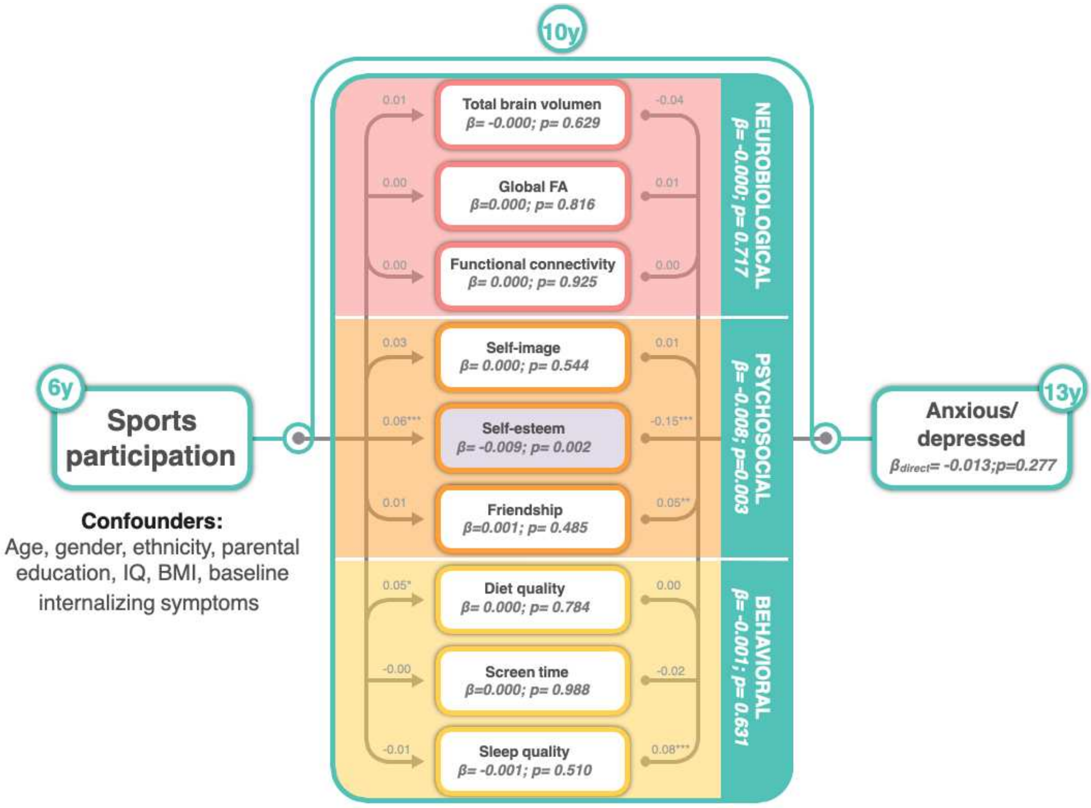


Figure S8. Integrative mediation model on the mechanisms linking sports participation and anxious/depressed mood in young people (n=4,216). BMI=body mass index; IQ= intelligence quotient; MD= mean diffusivity; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

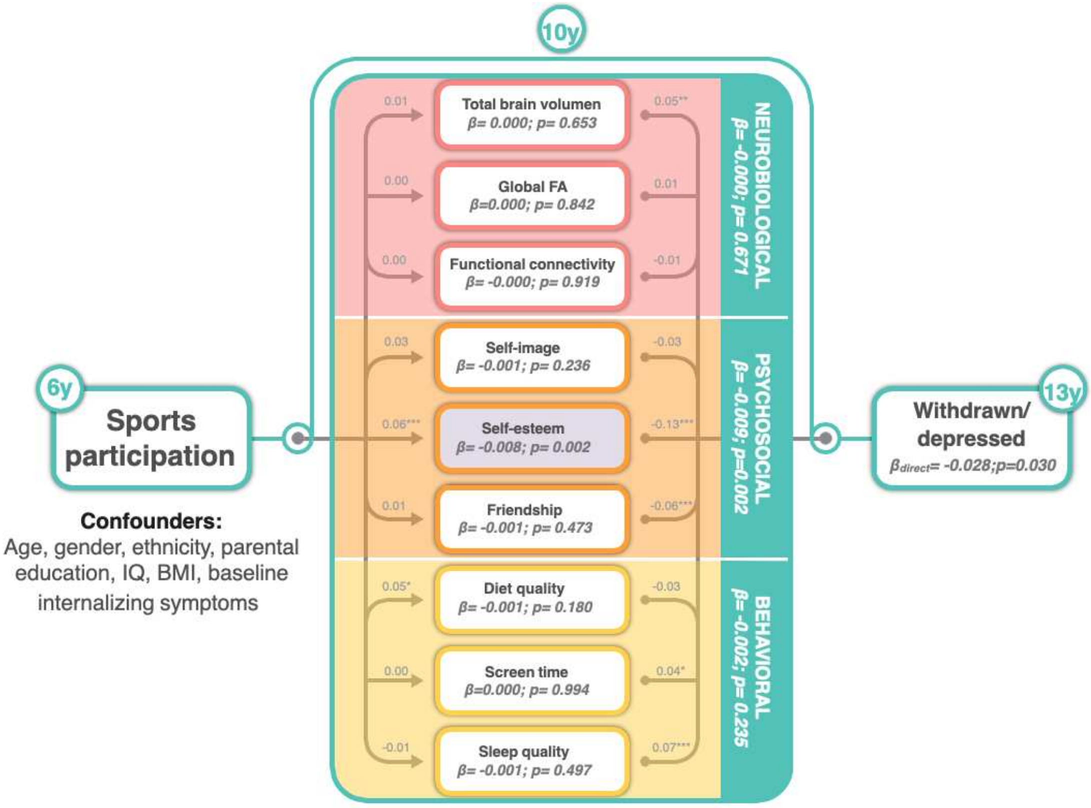


Figure S9. Integrative mediation model on the mechanisms linking sports participation and withdrawn/depressed mood in young people (n=4,216). BMI=body mass index; IQ= intelligence quotient; MD= mean diffusivity; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

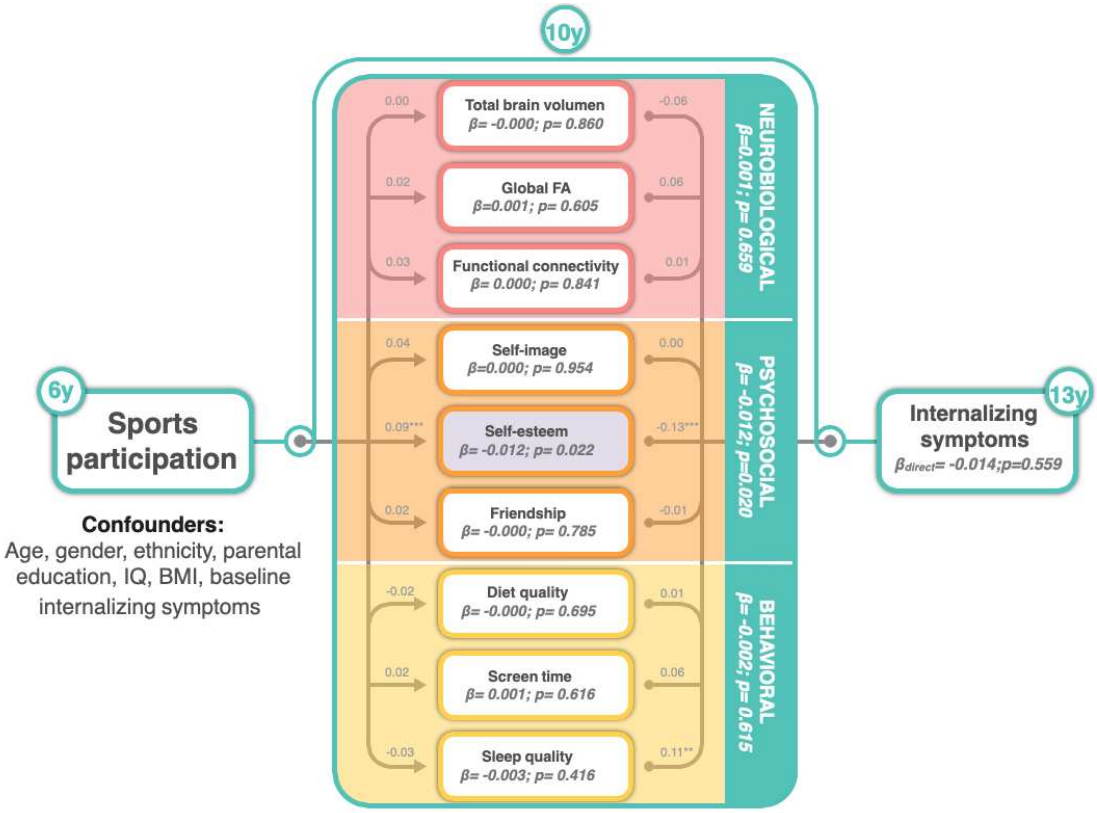


Figure S10. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in young people including only participant with complete data (n=1,025). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

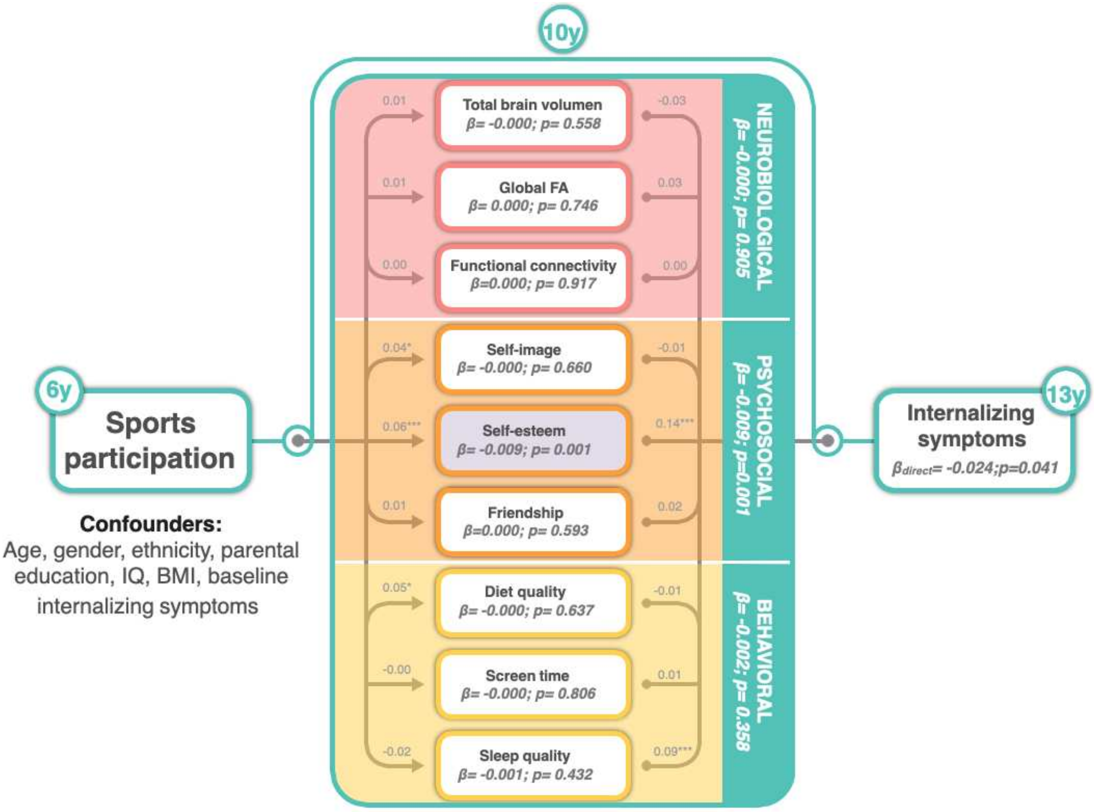


Figure S11. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in young people excluding siblings randomly (n=3,921). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old); β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

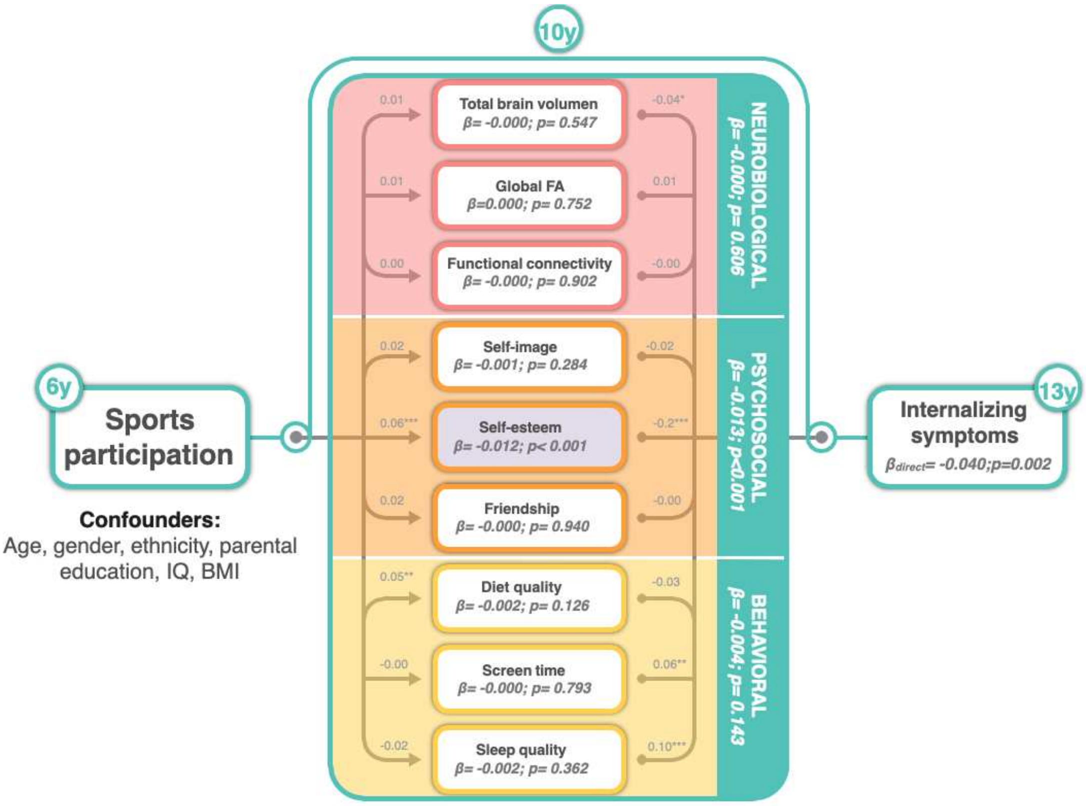


Figure S12. Integrative mediation model, without adjusting for internalizing symptoms at the baseline, on the mechanisms linking sports participation and internalizing symptoms in young people (n=4216). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

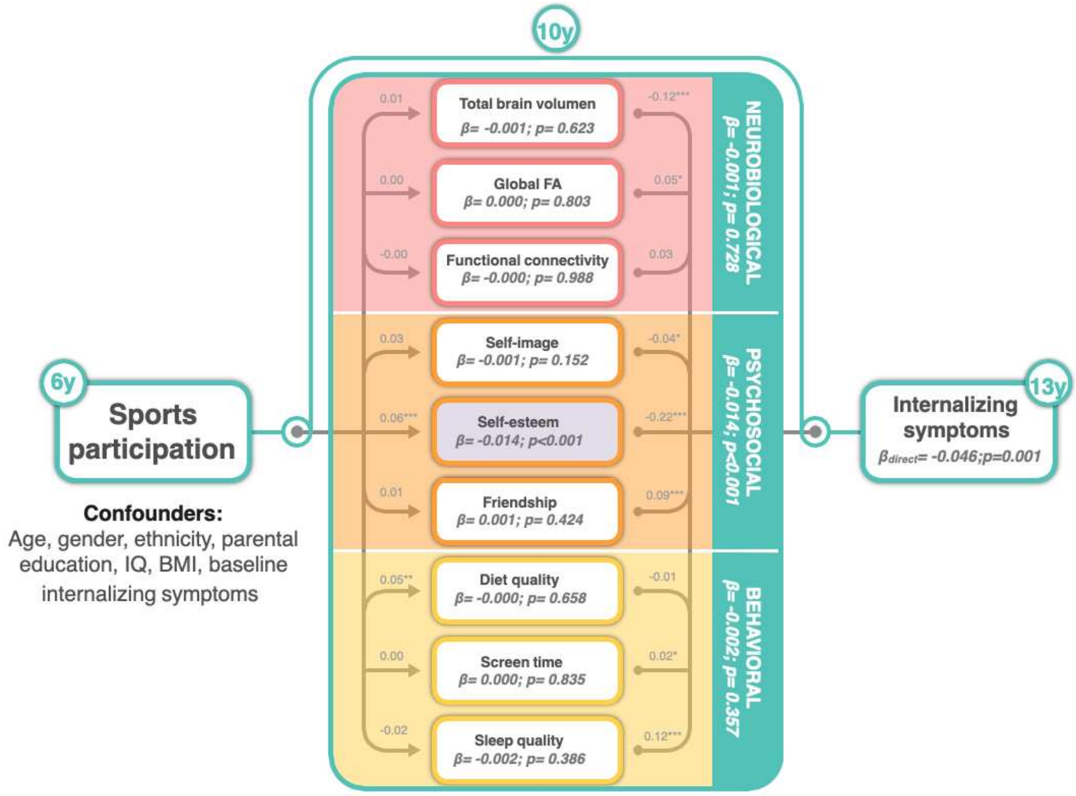


Figure S13. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in young people (n=4,060) with internalizing symptoms reported by the children instead of the primary caregiver. BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.

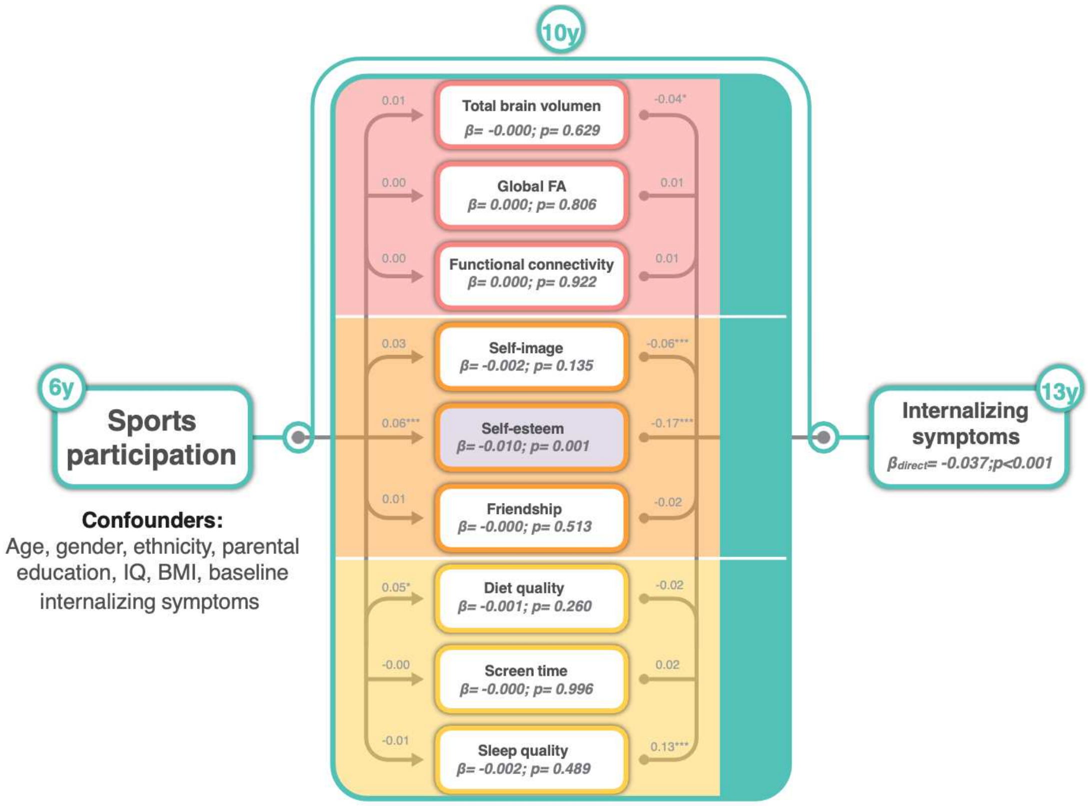


Figure S14. Mediation model including individually the mechanisms linking sports participation and internalizing symptoms in young people (n=4,060). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β values in the associations of sports participation with the mediators and the associations of the mediators with internalizing symptoms. * p <0.05, ** p<0.01, *** p<0.001.