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

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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.

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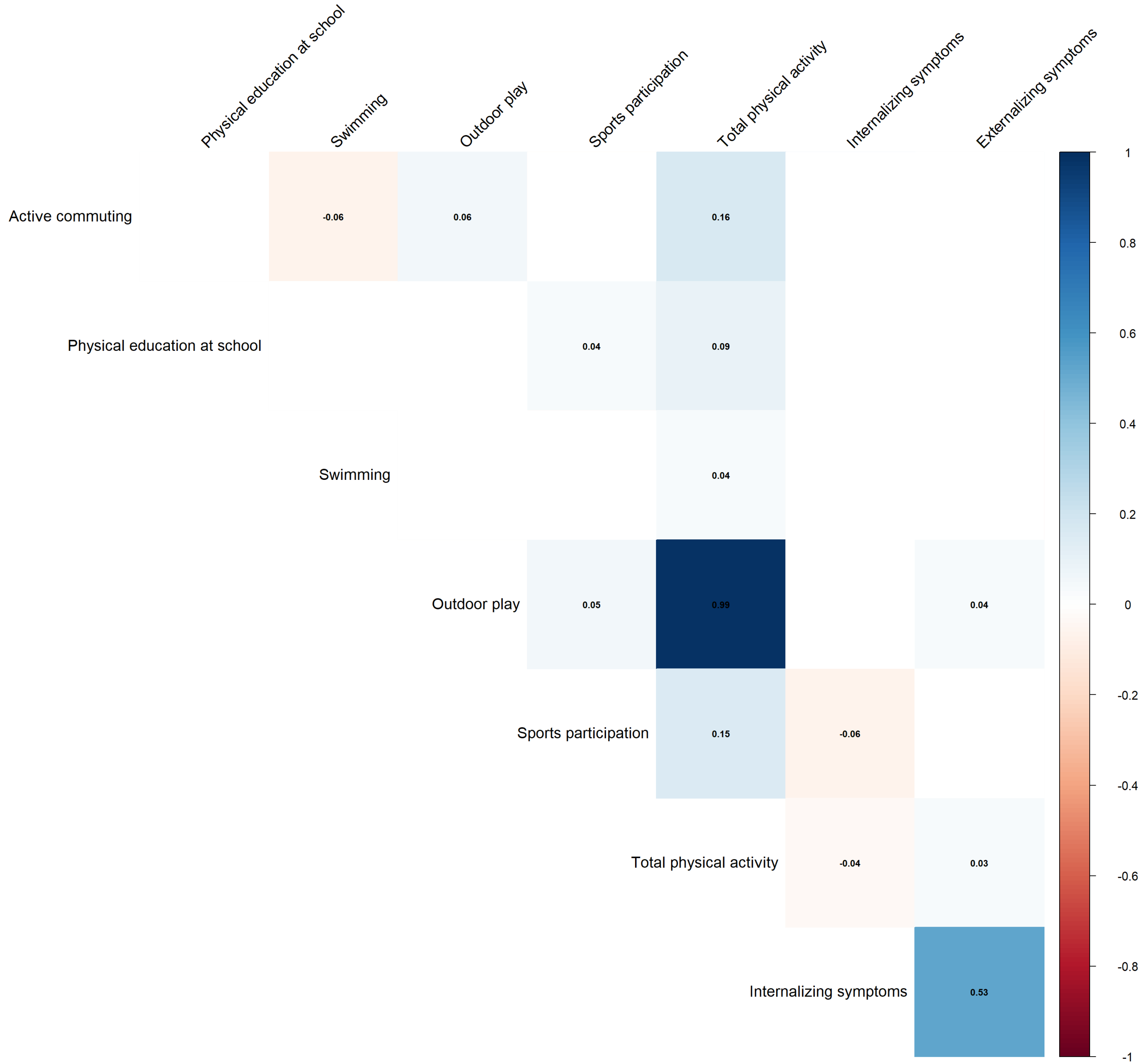
Table 1. Sample characteristics (n=4,216)

	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	

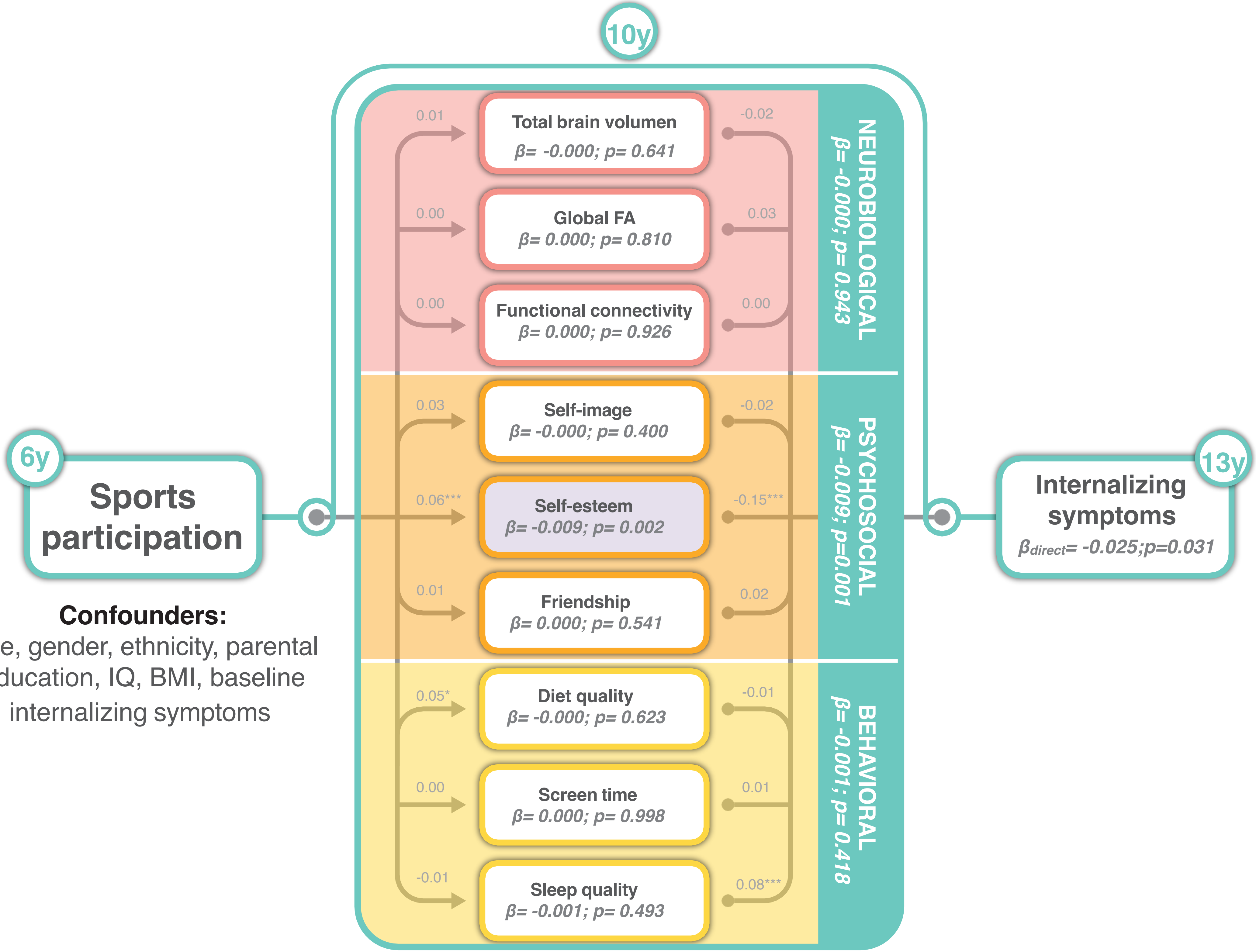
*Note: CBCL= Child Behavior Checklist school-age, IQ= intelligence quotient. Maternal education level was defined by the highest completed education and divided into 2 categories ranging from low (from no education to high school) to high education level (from higher vocational education to university). 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
Physical education at school
Swimming
Outdoor play
Sports participation
Total physical activity
Internalizing symptoms
-0.06
0.06
0.16
0.04
0.09
0.04
0.05
0.99
0.04
0.15
-0.06
-0.04
0.03
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).

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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.

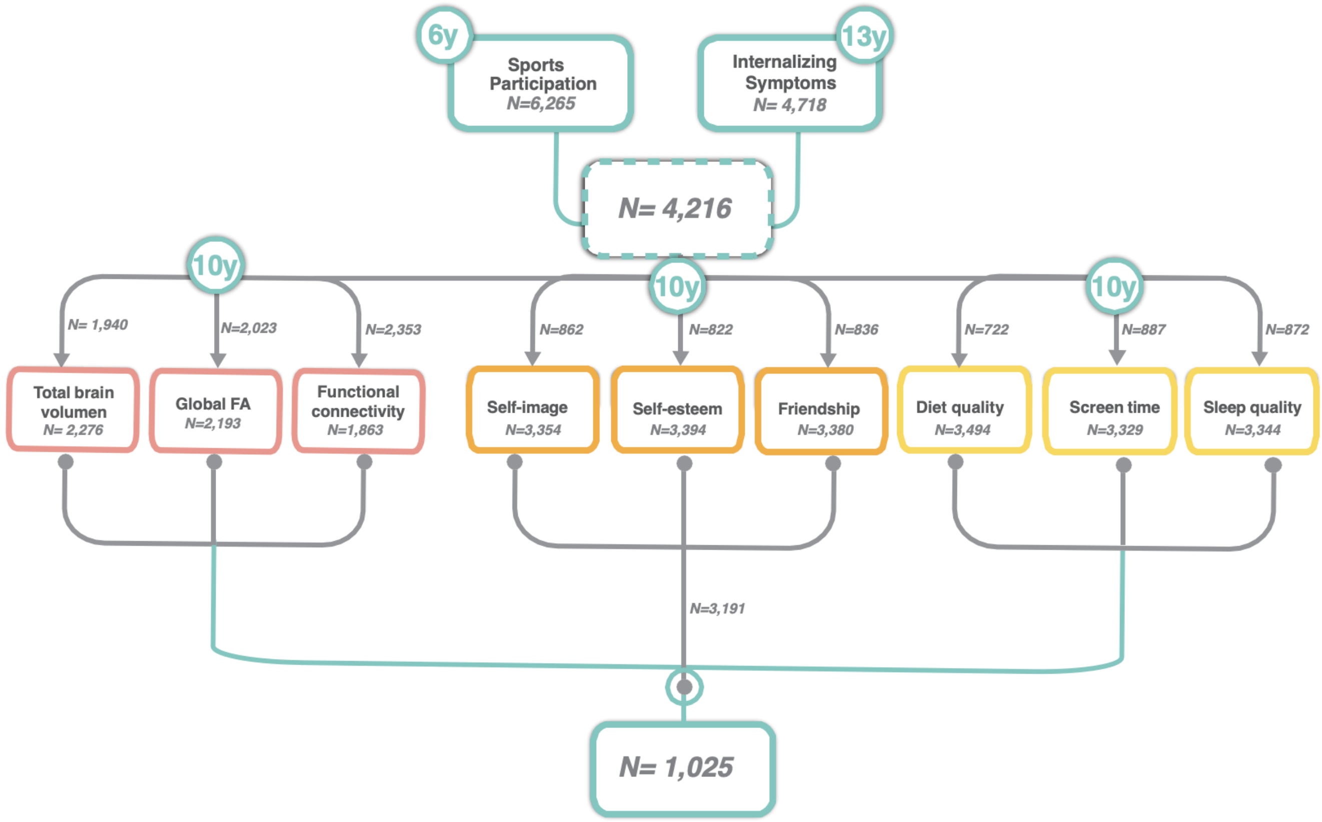

Figure S1. Flow chart. Box with dotted lines indicate the sample used in the main analysis. y=years old.

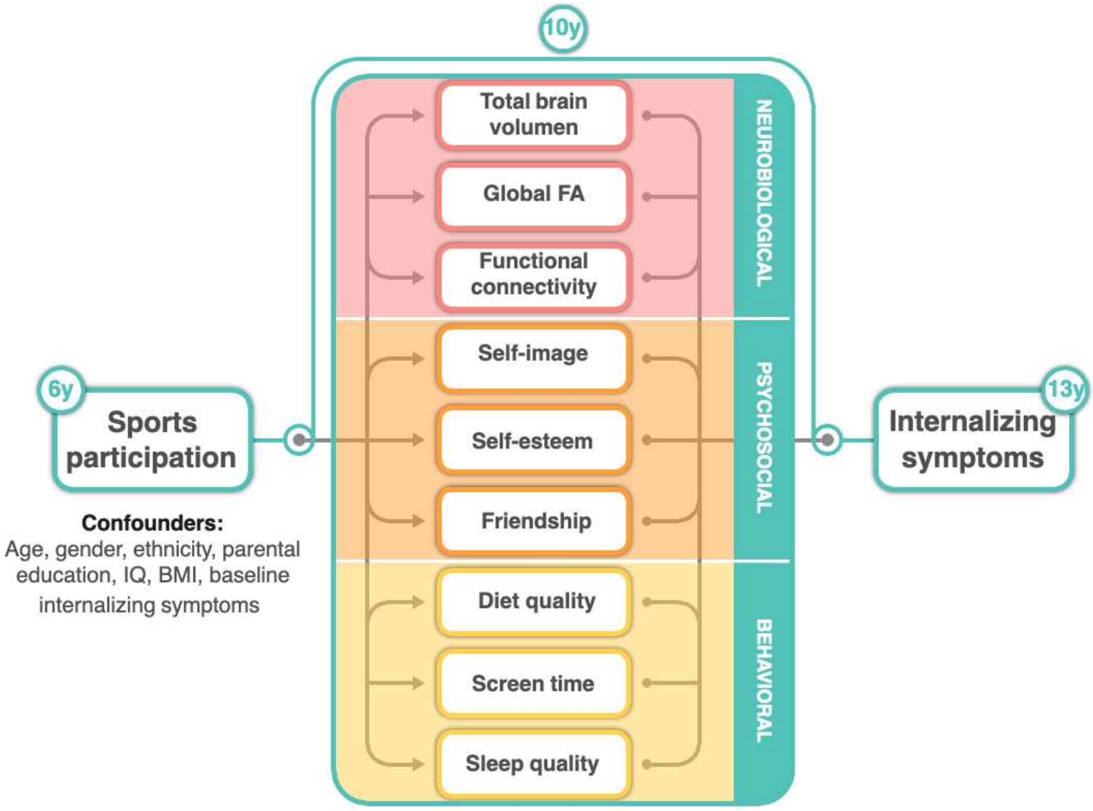

Figure S2. Visualization of the mediation modeling approach. BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old.

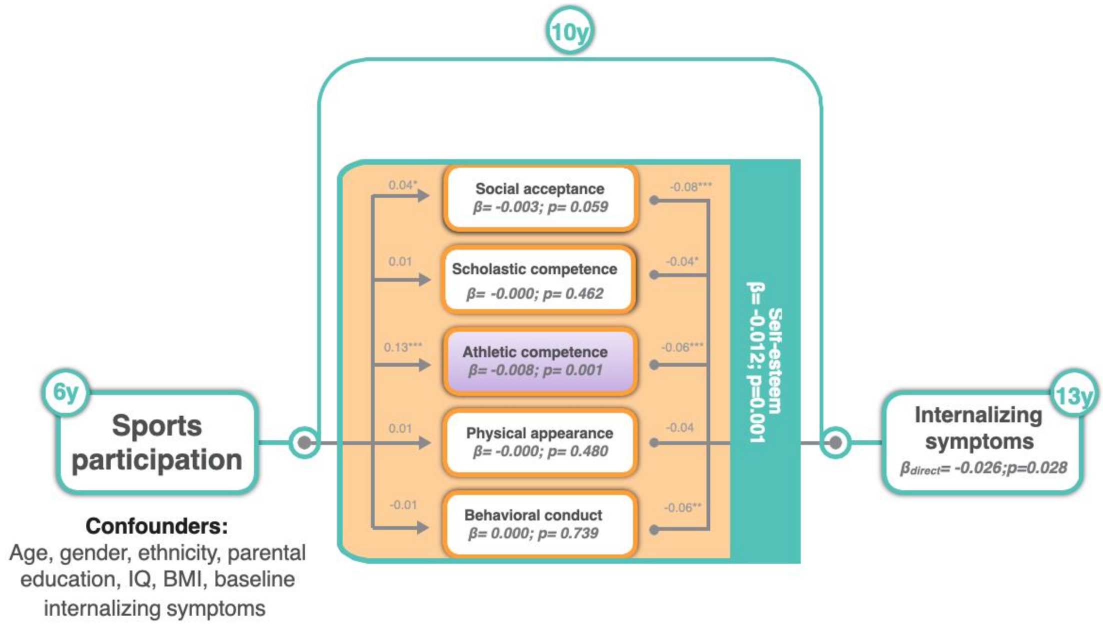

Figure S3. Integrative mediation model to explore the mediating role of self-esteem domains in the relationship between sports participation and internalizing symptoms in young people (n=4,216): a posteriori analysis. BMI=body mass index; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; 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.

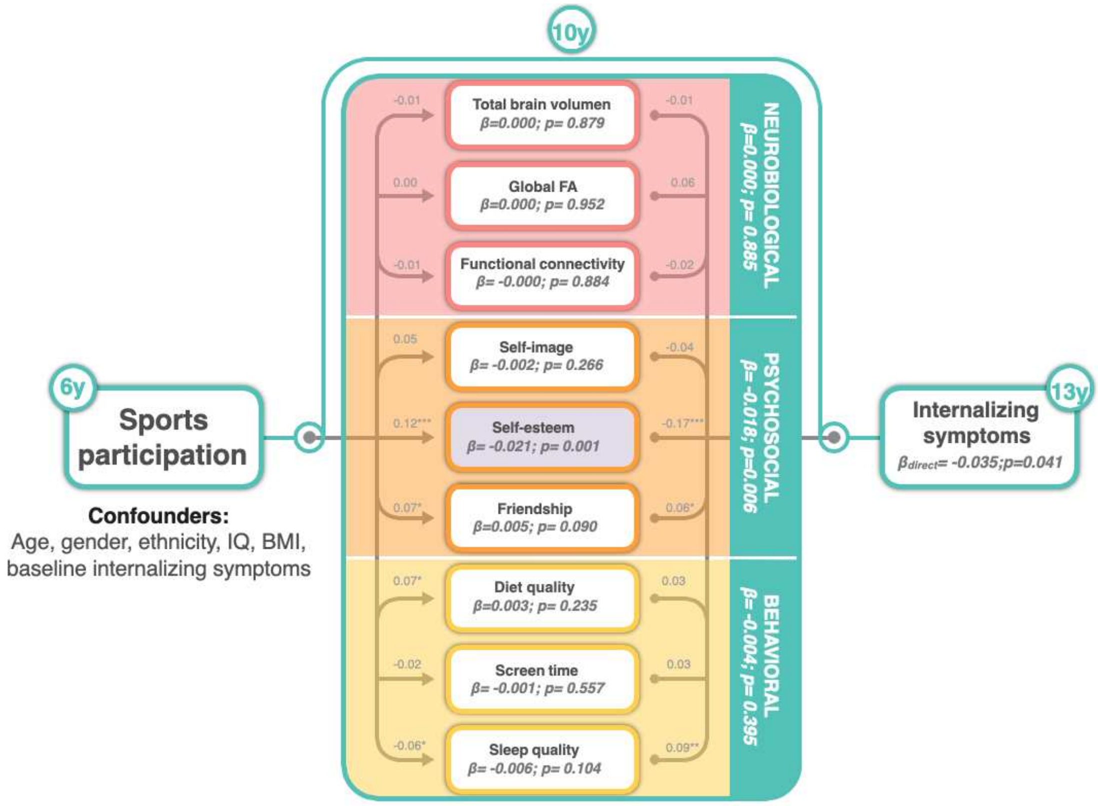

Figure S4. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in children who caregivers have a low educational status (n=1,543). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect 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.

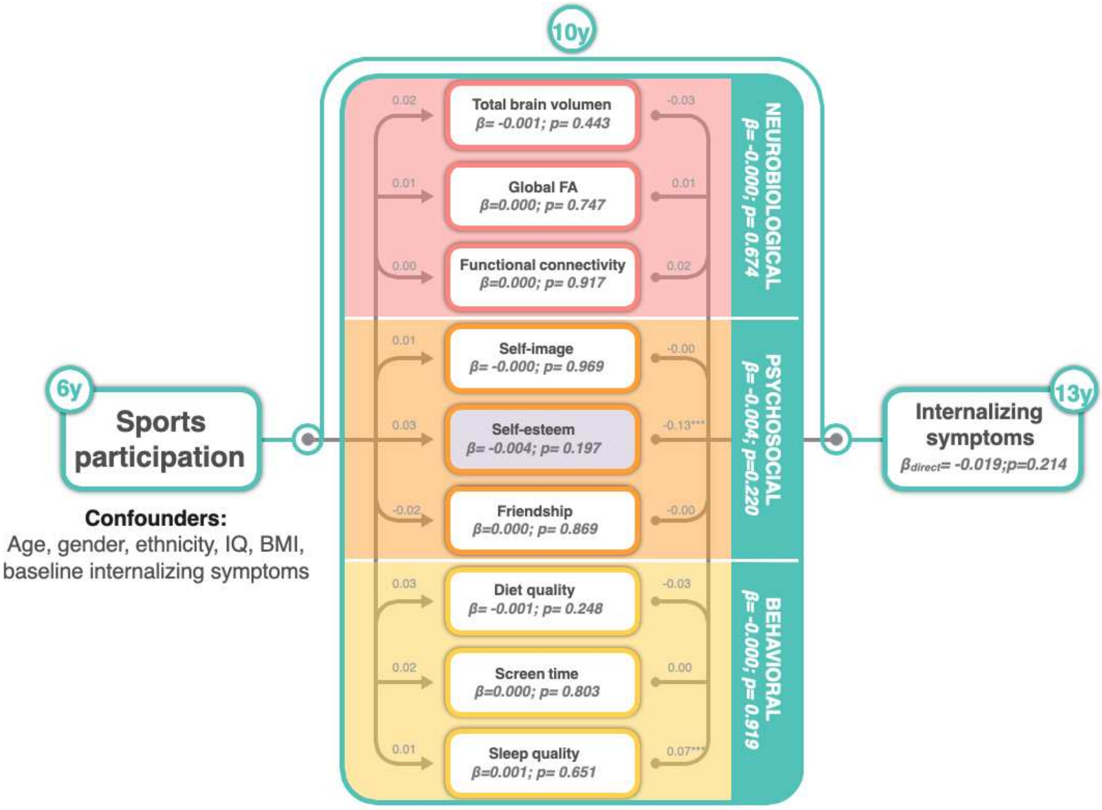

Figure S5. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in children who caregivers have a high educational status (n=2,670). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect 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.

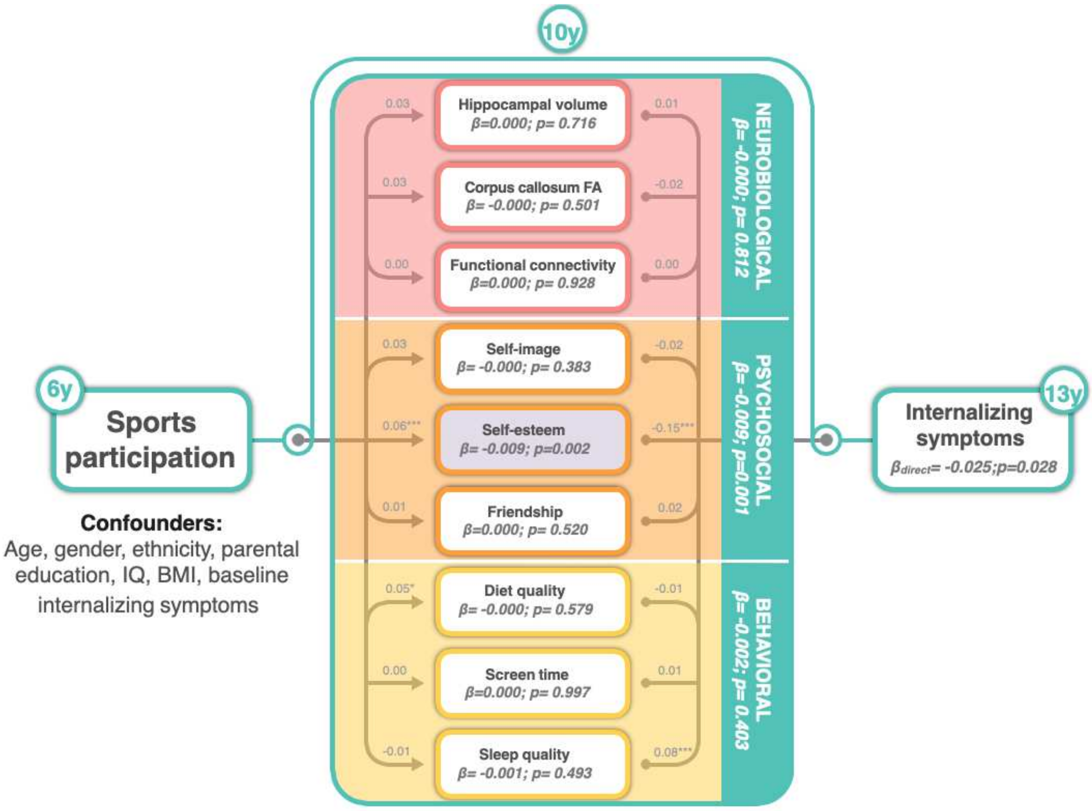

Figure S6. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in young people (n=4,216) including hippocampal volume and corpus callosum fractional anisotropy instead of global measures. BMI=body mass index; FA=fractional anisotropy; IQ= intelligence 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.

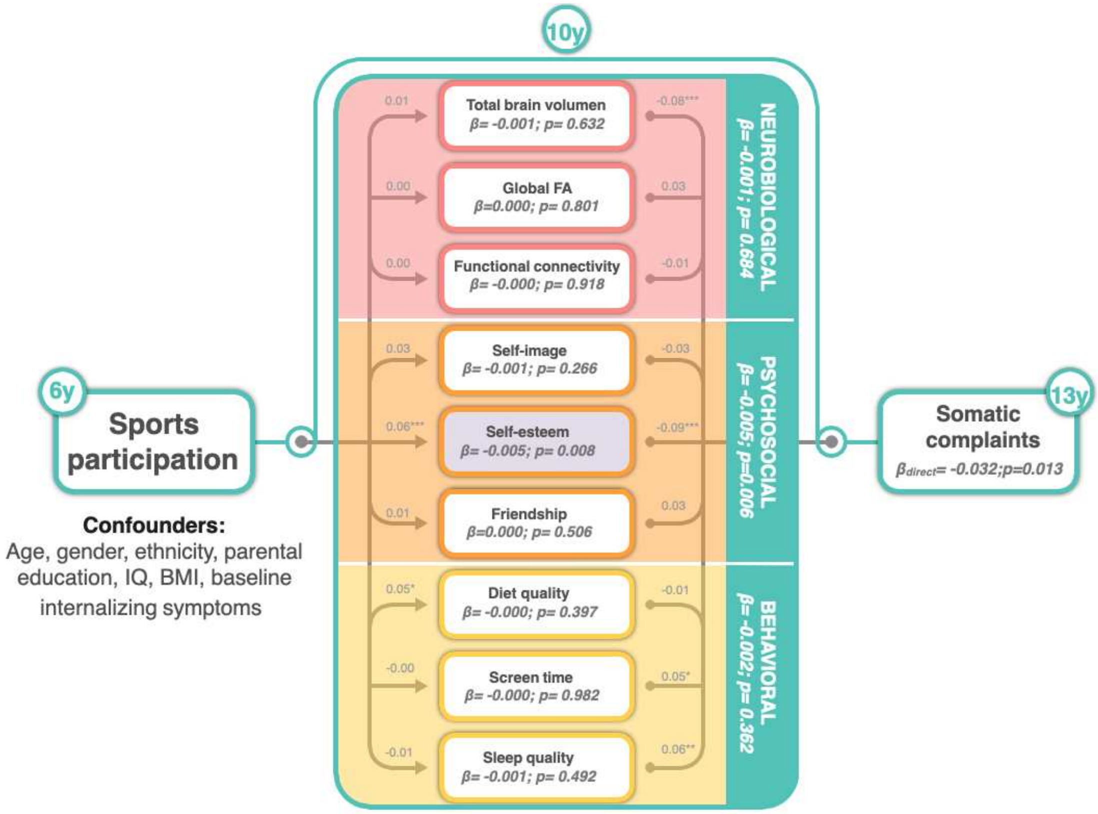

Figure S7. Integrative mediation model on the mechanisms linking sports participation and somatic complaints in young people (n=4,216). BMI=body mass index; IQ= intelligence quotient; MD= mean diffusivity; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the β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

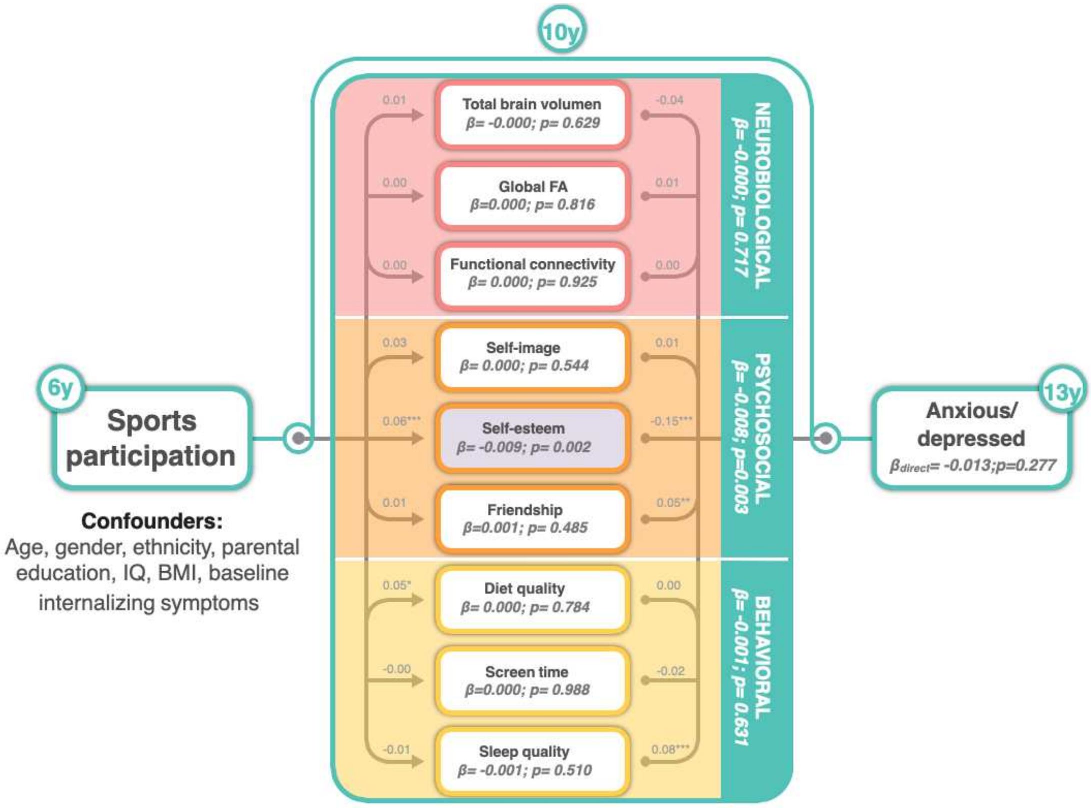

Figure S8. Integrative mediation model on the mechanisms linking sports participation and anxious/depressed mood in young people (n=4,216). BMI=body mass index; IQ= intelligence quotient; MD= mean diffusivity; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent the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

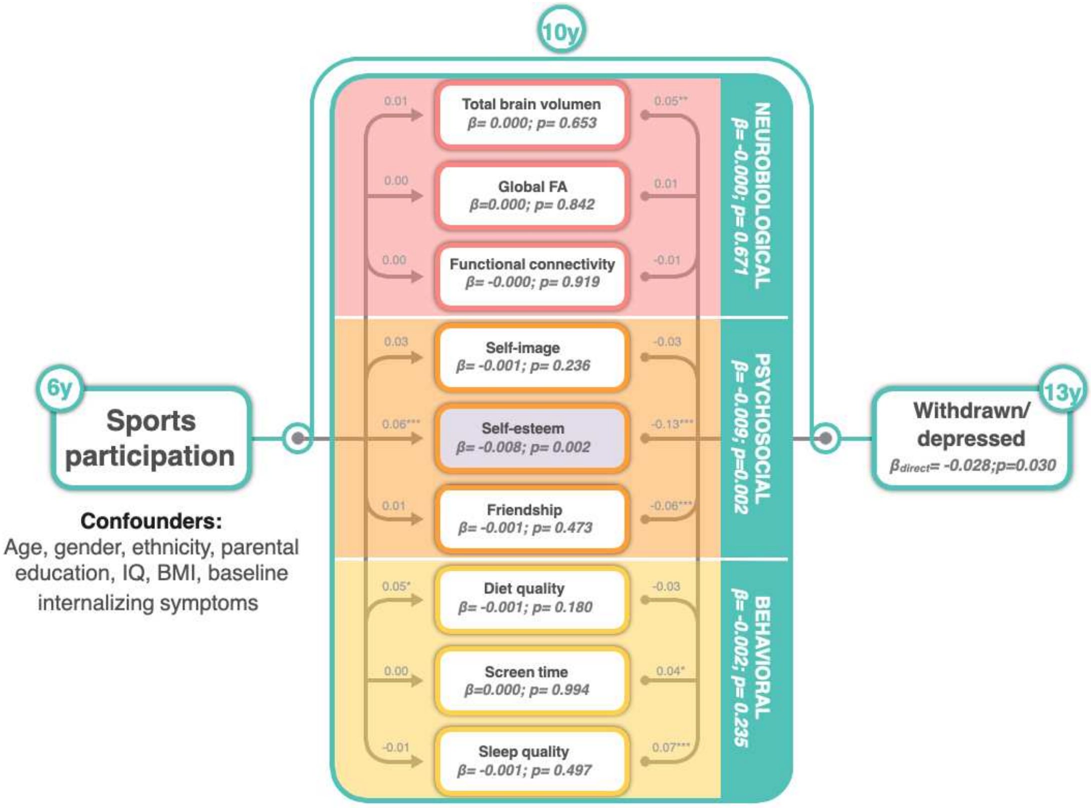

Figure S9. Integrative mediation model on the mechanisms linking sports participation and withdrawn/depressed mood in young people (n=4,216). BMI=body mass index; IQ= intelligence quotient; MD= mean diffusivity; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values represent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

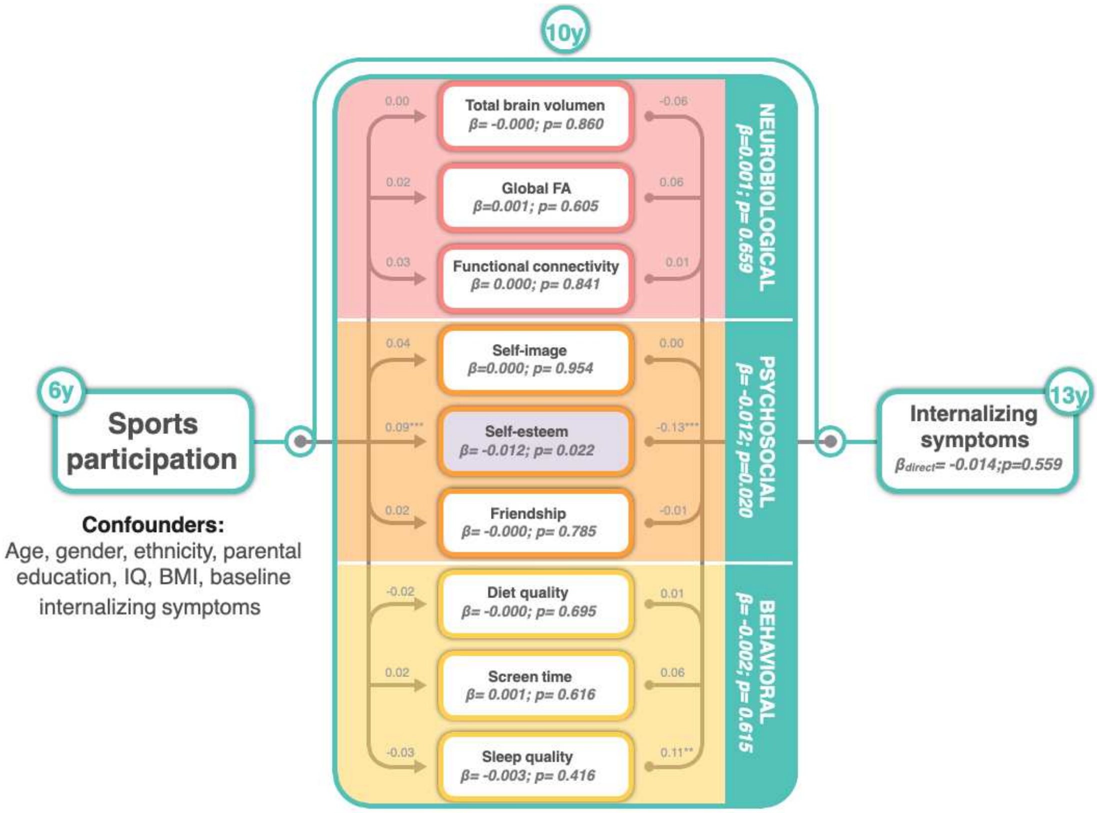

Figure S10. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in young people including only participant with complete data (n=1,025). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; 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.

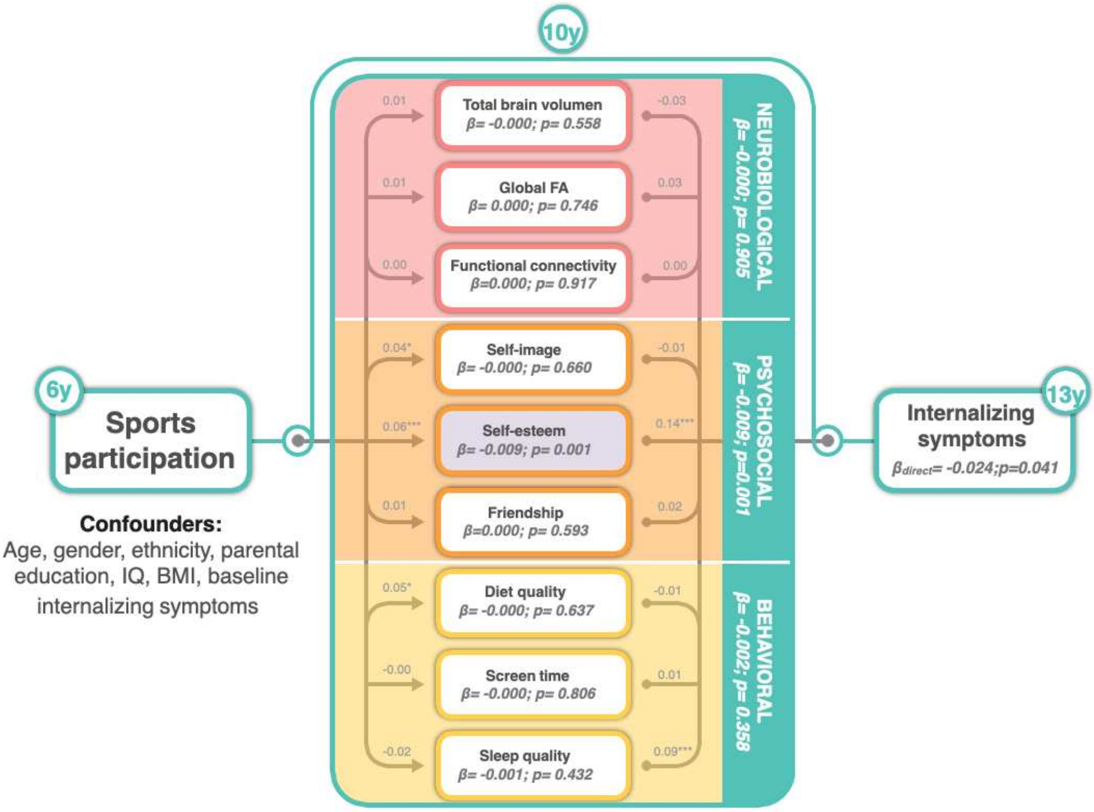

Figure S11. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in young people excluding siblings randomly (n=3,921). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old); β_{direct} = direct effect; β= indirect effect. 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.

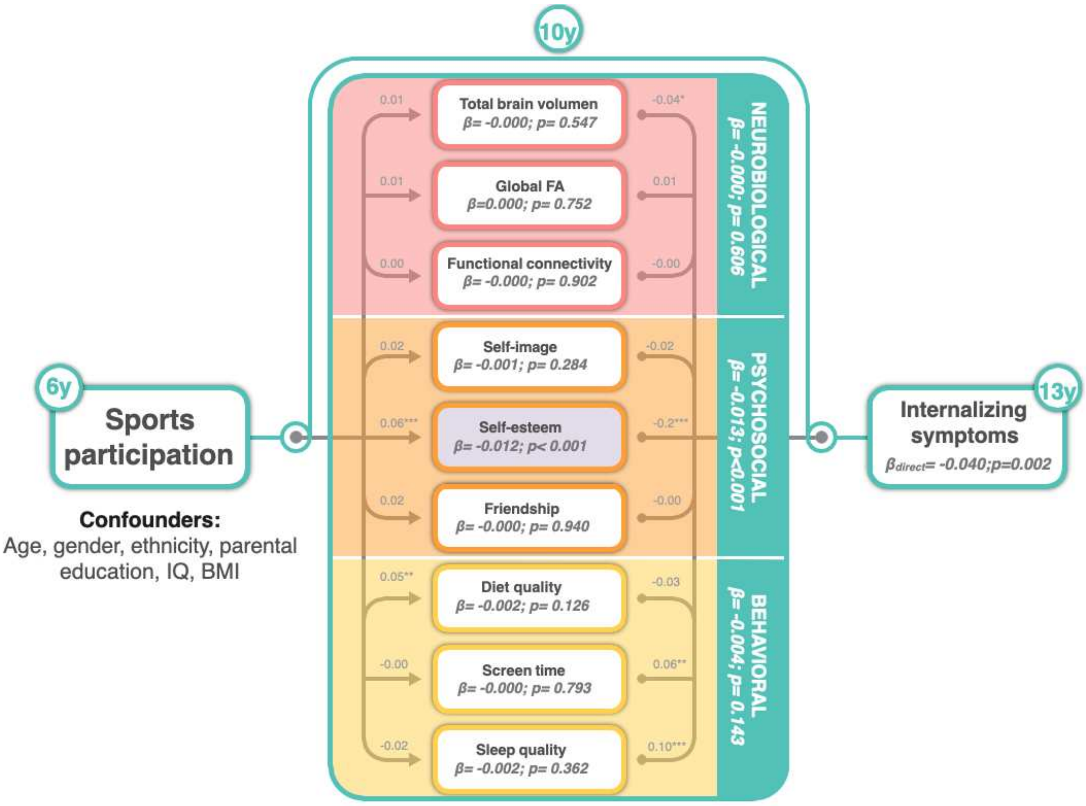

Figure S12. Integrative mediation model, without adjusting for internalizing symptoms at the baseline, on the mechanisms linking sports participation and internalizing symptoms in young people (n=4216). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = 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.

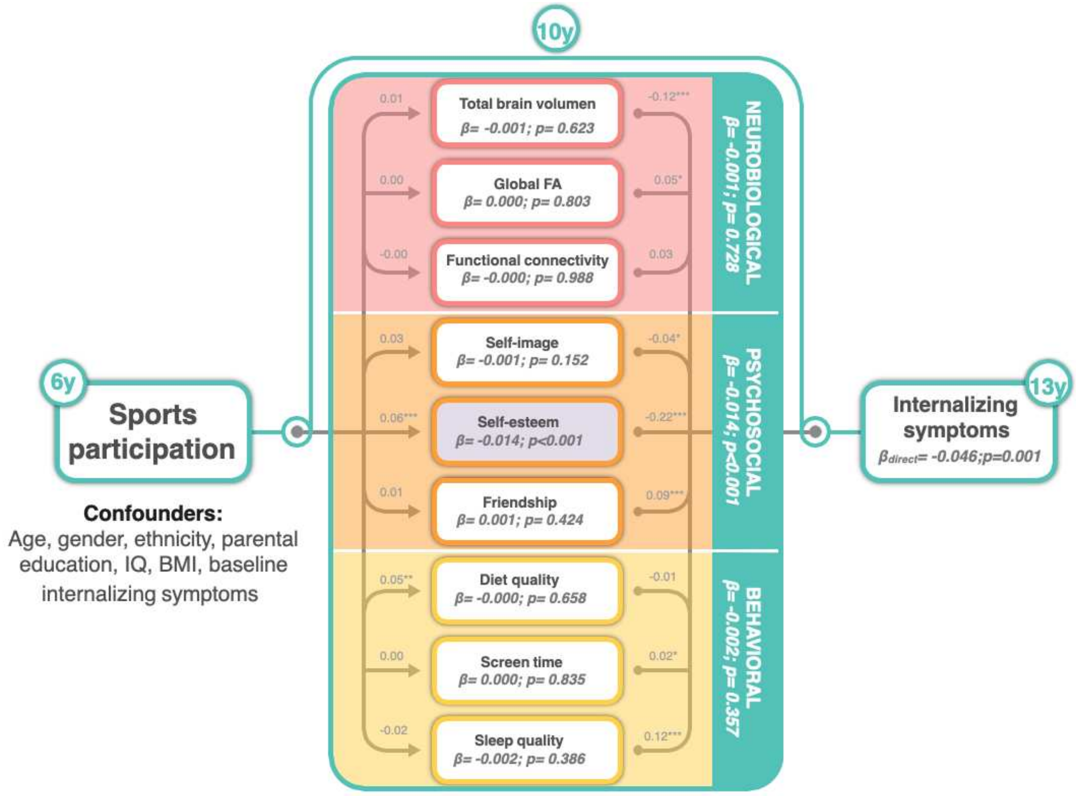

Figure S13. Integrative mediation model on the mechanisms linking sports participation and internalizing symptoms in young people (n=4,060) with internalizing symptoms reported by the children instead of the primary caregiver. BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; 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.

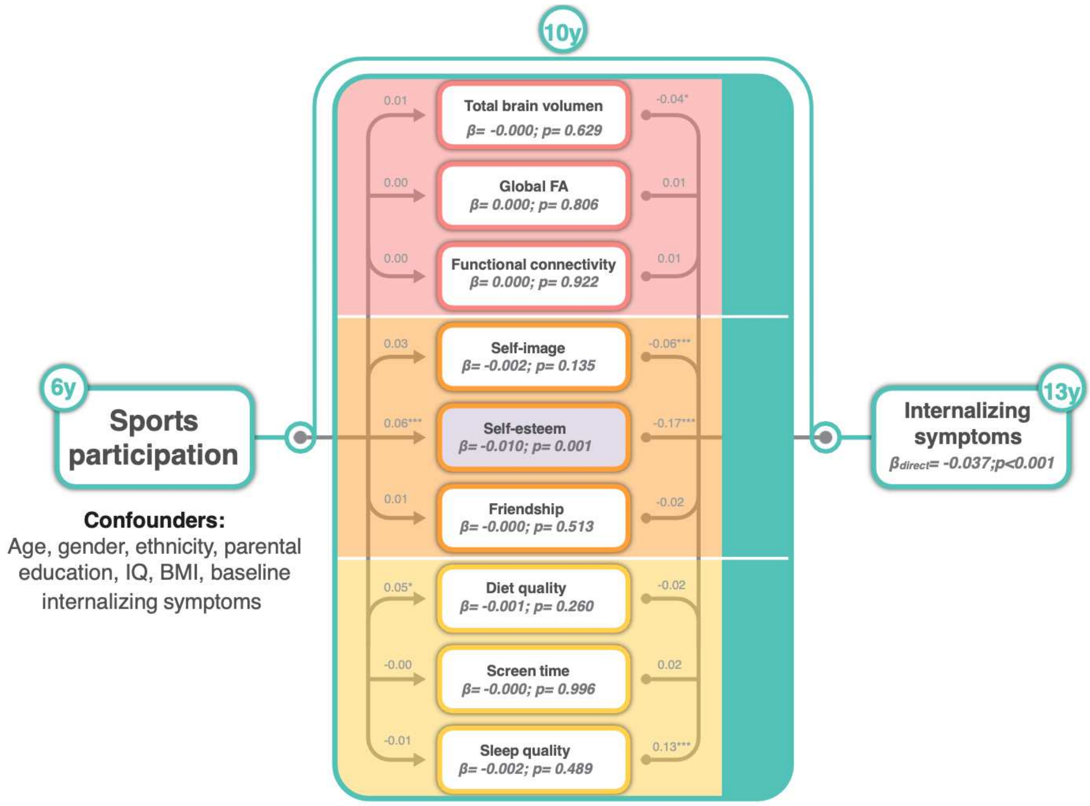

Figure S14. Mediation model including individually the mechanisms linking sports participation and internalizing symptoms in young people (n=4,060). BMI=body mass index; FA=fractional anisotropy; IQ= intelligence quotient; y=years old; β_{direct} = direct effect; β= indirect effect. Light grey values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