Ger J Exerc Sport Res 2022 · 52:282–289
https://doi.org/10.1007/s12662-022-00823-0
Received: 19 November 2021
Accepted: 22 April 2022
Published online: 6 May 2022

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The association of stress and physical activity: Mind the ecological fallacy

Introduction

Researchers are interested in the complex bidirectional relationship of psychological stress (PS) with physical activity (PA) as shown by the large number of studies, i.e., at least as much as 168 papers published in English language only within the past two decades (Stults-Kolehmainen & Sinha, 2014). Most of these studies ($n=124$; 73.8%) provide evidence that PS debilitates PA, i.e., a negative correlation. However, as 29 (17.3%) studies found an increase in PA related to PS (a positive correlation), the nature of the association between PS and PA is in question. The authors of a prominent systematic review in this field, Stults-Kolehmainen and Sinha submit several theoretical explanations for the ambiguous findings, e.g., a coping perspective to explain why stress predicted enhanced PA (Buman, Tuccitto, & Giacobbi, 2007; Stults-Kolehmainen & Sinha, 2014). Phrased in simple terms, people may become active to relieve stress. Based on the 17.3% of studies in the review that found an increase in PA associated with PS, findings in this direction cannot be termed anomalies. However, the authors also conclude, based on the 73.8% of studies that provide evidence for a negative correlation between PS and PA, that PS in general clearly has a negative effect on PA (Stults-Kolehmainen & Sinha, 2014). Beyond the possible explanations stated, for example, a negative relationship of PS and PA may also result from depleted mental and physical resources due to chronic stress and a positive relationship of PS and PA may also result from stress exposure in everyday life, such as many appointments that require PA to change locations. Accordingly, since understanding the behavioral mechanisms underlying distinct findings on the PS and PA association has important implications to tailor interventions and treatments, this is a critical topic for future endeavors.

The importance of this research in populations of children becomes evident against the background that childhood lays the foundation for lifelong physical activity behaviors, i.e., physical behavior in childhood has been shown to translate into adulthood (Dawson, Welde, & Harrell, 2000; Mäkelä, Aaltonen, Korhonen, Rose, & Kaprio, 2017; Pate, Baranowski, Dowda, & Trost, 1996). However, the majority of studies on the association of PS and PA investigated adult samples. One study in children found a negative correlation between PS and PA, but PS was associated with lower PA only in boys, not girls (McGlumphy, Gill, Shaver, Ajibewa, & Hasson, 2018). Overall, the lack of investigations on this PS–PA association in children is critical since insights such as whether PS hinders children from engaging in PA or vice versa, and whether PA in general is an important candidate for reducing stress among children is lacking evidence (Martikainen et al., 2013). Given the numerous health benefits of regular and frequent PA including increases in muscular strength (Leblanc et al., 2015), improved bone mineralization (Aly et al., 2004), cardiorespiratory fitness (Aires et al., 2010), greater brain volume and cognitive task performance (Chaddock-Heyman, Hillman, Cohen, & Kramer, 2014), lower risk of obesity (Hills, Andersen, & Byrne, 2011), and a lower metabolic risk profile (Gomes, dos Santos, Katzmarzyk, & Maia, 2017) on the one hand, and the detrimental effects of PS (Lagraauw, Kuiper, & Bot, 2015; Schönfeld, Brailovskaia, Bieda, Zhang,

Availability of data and material
The data and material that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability
The custom code used for the analyses of this study is available from the corresponding authors upon reasonable request.

& Margraf, 2016) on the other hand, emphasizes the need of studying how PS and PA are interrelated in children.

Taking a methodological perspective, we stumbled on the fact that large majority of studies on the association of PS and PA are of cross-sectional nature. Without any doubt, cross-sectional studies are of importance and have built a broad knowledge-basis in many research fields, also contributing to the understanding of the PS–PA association, mainly on temporally invariant predictors such as demographical and dispositional characteristics. However, often times, it has been discussed that cross-sectional studies harbor the risk of specific misinterpretation: the 'ecological fallacy' (Robinson, 2009). Accordingly, while both levels of analyses (between- and within-subject) can contribute to the understanding of associations of interest, researchers should carefully choose the analyses level depending on their specific research question.

For example, cross-sectional research can show that people who are more physically active are also those showing habitually lower blood pressure values, statistically a negative between-subject correlation. However, cross-sectional research cannot reveal that acute physical activity (such as climbing stairs) increases blood pressure, statistically a positive within-subject correlation (Kamarck, Schwartz, Janicki, Shiffman, & Raynor, 2003). To investigate the latter one, research gathering intensive longitudinal data within persons is indispensable. While using cross-sectional data as a shortcut to answering within-subject questions is intuitively appealing, within and between associations have been shown to be methodologically (Zawadzki, Smyth, Sliwinski, Ruiz, & Gerin, 2017), statistically (Zawadzki et al., 2017), and empirically (Kamarck et al., 2003) distinct and the directions of associations at these two levels can align, be unrelated, or even be in opposite directions.

Taking a methodological and statistical perspective, Molenaar (2004) could show that specific assumptions named "ergodicity", e.g., all population means, variances, and covariances being identical to the within-person values, have to be met for generalization of findings from the between to the within-subject level (Hamaker, 2012; Molenaar, 2004). From an empirical perspective, many behavioral phenomena are of non-ergodic nature, i.e., the between and within subject level do not align to each other, which has been shown multiple times (e.g., Liao, Chou, Huh, Leventhal, & Dunton, 2016). Here, the within-person perspective is of high importance to focus on change via treatments and interventions. In particular, between-person associations are important, e.g., to enable for risk stratification, but cross-sectional data do not provide information on within-subject mechanism of action potentially being modifiable via individually tailored interventions.

Translated to practice, if one is interested in the reasons of a child experiencing PS at a certain daytime or in a specific context, between-subject research is limited for the above-mentioned reason and vice versa, within-subject data is limited in unraveling how PS and PA interact with time invariant predictors (e.g., sex, socioeconomic status). While in sociology, the issue of the ecological fallacy traces back to the year 1950, when Robinson published the first prominent paper being cited more than 7000 times to date (Robinson, 2009), and in psychology, these accounts and its statistical foundations have been intensively researched for the last 20 years (e.g., Molenaar, 2004) applying the methodological distinction of between versus within subjects may still remain an open issue in some areas, e.g., including the research on association of PS and PA in everyday life.

Thus, we wondered whether the different valence of the association between PS and PA may in parts be explained by the ecological fallacy, i.e., by distinct levels of analyses. To tackle this issue, we gathered intensive longitudinal data from children aged 7–11 years, a thus far highly understudied population regarding the effects of PS on PA (Stults-Kolehmainen & Sinha, 2014), and conducted both within-subject and between-subject analyses simultaneously applying a multilevel model.

Methods

Study participants

To investigate whether the level of analyses (between- vs. within-persons) is indeed relevant to the effect of PS on PA, the psychiatric–epidemiological center (PEZ) at the Central Institute of Mental Health in Mannheim (CIMH), Germany, recruited a sample of 99 children aged 7–11 years randomly from local population registers from 2014–2016. Participants were selected by specific stratifications such as gender and ethnic background. Exclusion criteria included the following: acute diseases, mental disorders, cardiovascular disorders, chronic endocrine or immunological diseases. Detailed recruitment information can be found elsewhere (Reichert et al., 2016).

Study procedures

Across 7 days in their everyday life, children carried an accelerometer (movisens move-2/3; (Movisens GmbH, n.d.)) at the right side of their hip during wake times. Additionally, the children reported at the end of each day (before bedtime) their PS of the day on an established 61 item questionnaire (Traue, Hrabal, & Kosarz, 2000). The so-called Alltags-Belastungsfragebogen is the German version of the daily stress inventory (Brantley, Waggoner, Jones, & Rappaport, 1987) and assesses the number and intensity of stressful events during the day, which has been shown to be appropriate for assessing daily fluctuations in PS and revealed sound psychometric properties of Cronbachs $\alpha = 0.94$, indicating a high internal consistency (Traue et al., 2000). In the present study, we received a McDonald's omega of 0.96 referring to the total score across 7 days. Examples of the type of captured daily hassles include not being able to sufficiently complete a task, being misunderstood, losing a (sports) game, missing an appointment, being involved in a dispute, bad weather and disturbed sleep.

Together with their parents and prior to the assessment week, children received an extensive briefing and individual training how to handle the accelerometer and how to fill out the questionnaires at the PEZ. Parents were instructed to provide their children with help in filling out the questionnaire and in attaching the accelerometer in everyday life if necessary. We excluded 20 datasets due to missing accelerometer data, i.e., lost devices, technical errors; 5 datasets were excluded because of incomplete questionnaire data. In particular, we excluded data of participants with more than 30% missing data (i.e., less than 3 of 7 days of valid assessment data (Trull & Ebner-Priemer, 2020)). Thus, the final dataset comprised data from 74 children (42 female) with a mean age of 9.81 years (standard deviation [SD] = 1.66). The children wore accelerometers positioned on the right hip across the entire study period yet not during sleep times. The acceleration sensors (movisens move-3 or -4; Movisens GmbH, Karlsruhe, Germany) captured triaxial movements with a measurement range: ±8 g, a sampling frequency of 64 Hz, and a resolution of 12 bits. These devices have been validated to be appropriate for capturing human PAs (Anastasopoulou et al., 2014).

Data preprocessing

To calculate the average PA each child engaged in across each day, we followed established procedures as previously reported (Reichert et al., 2017; and von Haaren et al., 2016) and preprocessed the accelerometer data by calculating the mean movement acceleration intensity (MAI; using the software data analyzer (version 1.6.12129; Movisens GmbH, n.d.)). MAI represents the vector magnitude of acceleration captured at the sensor axes in milli-g ([g]/1000). In particular, MAI is computed through eliminating gravitational components (high-pass filter at 0.25 Hz) and eliminating artifacts (such as vibrations of cycling rough roads and external sensor shocks; low-pass filter at 11 Hz) (Reichert et al., 2017; von Haaren et al., 2016). We merged the accelerometer and questionnaire data with a day-level resolution using the software SPSS, version 26 (SPSS Modeler—Überblick—Deutschland | IBM, n.d.).

Abstract

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The association of stress and physical activity: Mind the ecological fallacy

Abstract

Psychological stress and physical activity are interrelated, constituting a relevant association to human health, especially in children. However, the association's nature remains elusive, i.e., why psychological stress predicts both decreased and increased physical activity. To test whether effects vary as a function of the level of analyses, we derived intensive longitudinal data via accelerometers and stress questionnaires from 74 children across 7 days as they went about their daily routines ($n = 513$ assessments). Multilevel modelling analyses revealed that between children, higher psychological stress predicted decreased physical activity (standardized beta coefficient = –0.14; $p = 0.046$). Concurrently, within those children, higher psychological stress predicted increased physical activity across days (standardized beta coefficient = 0.09; $p = 0.015$). Translated to practice, children who experienced more stress than others moved less, but children were more active on days when they experienced heightened stress. This suggests that the analyses level is crucial to the understanding of the association between psychological stress and physical activity and should be considered to receive unequivocal results. If replicated, e.g., including high-frequency sampling and experimental manipulation in everyday life for in-depth insights on underlying mechanisms and causality, our findings may be translated to individually tailored (digital) prevention and intervention strategies which target children's distress-feelings despite impairing their heightened physical activity in stressful situations and identify tipping points of chronic stress phases. Therefore, we especially call for more intensive longitudinal data approaches to tackle thus far neglected within-subject issues in the field of physical activity, sport and exercise research.

Keywords

Ambulatory Assessment · Accelerometry · Ergodicity · Within-subject perspective · Intensive Longitudinal Data

Statistical analysis

We applied multilevel modeling and fitted a linear mixed effects model nesting daily PA measures (level 1) within children (level 2) using the software SPSS (SPSS Modeler—Überblick—Deutschland | IBM, n.d.). We set the alpha level to 0.05 and entered fixed effects of daily psychological stress (sum number of daily hassles) as within-person predictor (level 1) and total psychological stress (mean number of daily hassles across the study week) as between-person predictor into our model. In particular, following the idea formulated by Curran and Bauer (2011), we estimated the effects of the within-subject predictor daily PS, which we within-subject centered on each person's mean PS score (averaged across the study week, respectively), and the between-subject predictor mean daily PS, i.e., each person's mean daily PS score (averaged across the study week, respectively), simultaneously within one model (Curran & Bauer, 2011). We entered gender as a covariate into our model as there is profound evidence that stress impacts boys and girls distinctly, see "Introduction" section and McGlumphy et al. (2018). The final model is presented in Eq. 1.

Equation 1:

$$
\begin{aligned}
& Y\,(Physical\,Activity)_{ij} \\
&= \beta_{00} + \beta_{10} \cdot \text{perceived daily stress}_{ij} \\
&\quad + \beta_{01} \cdot \text{perceived total stress}_{ij} \\
&\quad + \beta_{02} \cdot \text{gender}_{ij} + \mu_{ij} + r_{ij}
\end{aligned}
$$

Here, within-subject effects were estimated from childrens' PA measurements (subscript j) along measurement time points (i.e., days; subscript i): The PA level in participant j at time i is depicted by Y_{ij}, respectively. The intercept and the effects of daily psychological stress (level 1) as well as between-subject effects (level 2) of total psychological stress and gender are depicted by the beta coefficients; r_{ij}

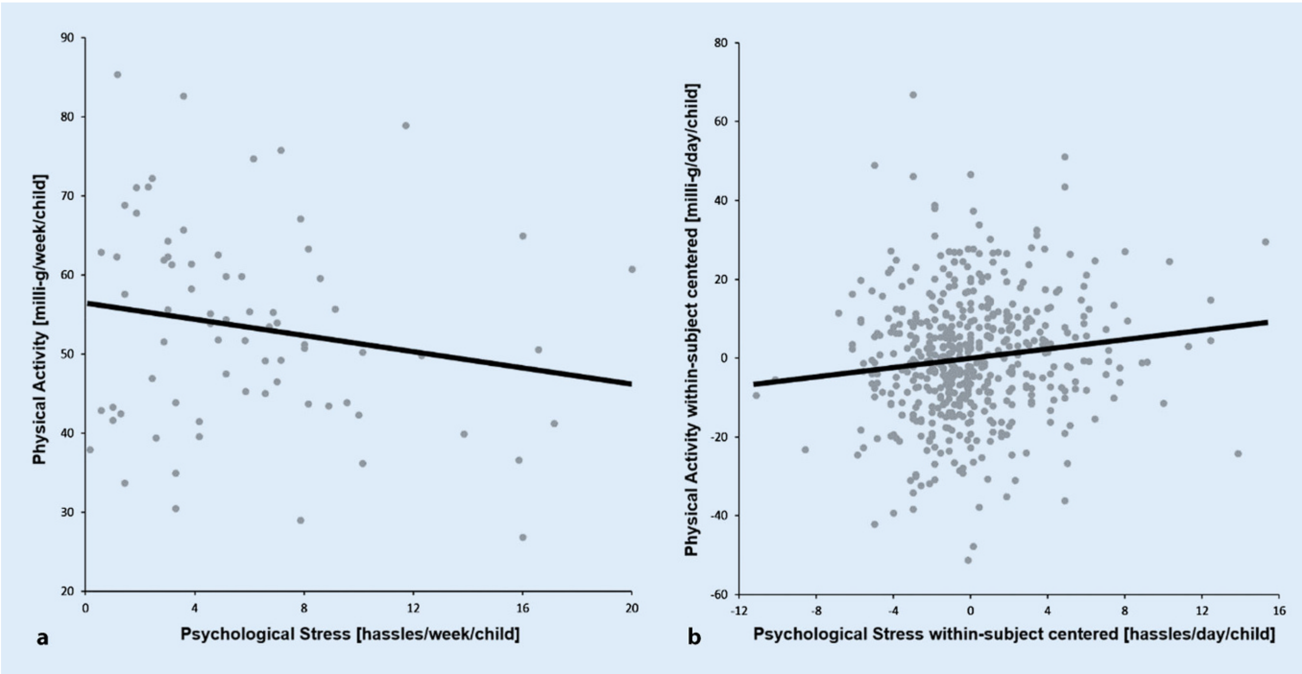

Fig. 1 ▲ The negative between-person (**a**) and positive within-person (**b**) association of psychological stress (PS) and physical activity (PA) in 74 children. **a** Scatterplot with regression line (*black line*), **b** estimated mean effect of PS on PA within the typical subject (*black line*). For better visualization of the within-subject association, values on the PS (x-axis) and PA (y-axis) were centered on each subject's mean (**b**). Please note that the outcome-centering was only done for visualization purposes yet the multilevel model computed contains the uncentered PA variable (see "Methods" section)

indicates the level 1 residuals and μ_{ij} random effects (individual effect-variations around the fixed effect). Accordingly, we included random effects for the intercept. Since ignoring potential autocorrelations violates statistical assumptions, we modeled autoregressive error terms. Intraclass correlation coefficients were calculated using null models. To standardize beta coefficients, we followed an established procedure published by Hox, Moerbeek, & van de Schoot (2017).

Our model detected 37.3 and 70.5% variance due to within-person variation in PS and PA (intraclass correlation coefficient [ICC] = 0.627 and 0.295) and 62.7 and 29.5% variance due to between-person variation in PS and PA. The average PA activity levels of our participants (movement acceleration intensity [MAI] per participant per week = 53.39 milli-g) and the average PS (M = 6.06; range: 0.17–20; SD = 4.47 milli-g) were in line with data from other healthy cohorts (Da silva et al., 2014; Traue et al., 2000).

Ethical considerations

Our study was approved by the Medical Ethics Committee of Heidelberg University, Germany. Parents gave written informed consent for their children, who received monetary compensation of 100 € for their effort.

Results

Cross-sectionally, children with higher PS showed decreased PA, i.e., children who experienced more stress than others moved less (standardized beta coefficient = –0.14; $p = 0.046$; **Fig. 1a** and **Table 1**). However, on average, higher PS predicted increased PA within children (standardized beta coefficient = 0.09; $p = 0.015$; **Table 1**), i.e., participants were more active on days when they experienced heightened stress (**Fig. 1b**). For a child of our sample who experienced relatively high stress across the study week, i.e., our between-subject predictor being "20", compared to a child who experienced no stress at all across the study week, i.e., our between-subject predictor being "0", our model estimated a decreased PA level of −13.12 milli-g.

Given that the mean PA level of our cohort was 53.39 milli-g (range: 26.92–85.38; SD = 12.77 milli-g), which is comparable to other healthy cohorts of this age group (Da silva et al., 2014), this estimate indicates a considerable negative effect of PS on PA between subjects. Moreover, for the typical child of our sample, our model estimated on days with relatively high (above-person-average) stress (i.e., the within-subject centered predictor being "+10") compared days relatively low (below-person-average) stress (i.e., the within-subject centered predictor being "−10") an increase of her/his PA level of 11.11 milli-g. Again, this estimate indicates a considerable positive effect of PS on PA within subjects.

In an exploratory step, we tested for cross-level between–within interactions. In particular, hypothesizing a moderating role of chronic stress on the relationship between PS and PA, we introduced a cross-level interaction

Table 1 Multilevel model analysis: fixed and random effects

Outcome	Fixed				Random			
Predictor	Beta coefficient (CI[a])	Standard error	t-Value (df[b])	*p*-Value	Variance estimate	SE	Wald-Z	*p*-Value
Intercept	61.309 (55.10; 67.52)	3.114	19.69 (70.89)	<0.001	94.236	26.37	3.574	<0.001
Gender [female][c,d]	−6.909 (−12.68; −1.13)	2.896	−2.38 (70.59)	0.02	–	–	–	–
Daily psychological stress [hassles/day/child][e]	0.556 (0.109; 1.00)	0.227	2.45 (402.68)	0.015	–	–	–	–
Total psychological stress [hassles/week/child][d]	−0.656 (−1.301; −0.01)	0.323	−2.03 (70.58)	0.046	–	–	–	–

[a]Lower and upper confidence intervals (CI)
[b]Degrees of freedom
[c]Reference category: male
[d]Between-subject predictor
[e]Within-subject predictor

PS (between-subject) ×PS (within-subject) into our multilevel model which yielded a null result ($p = 0.61$).

Discussion

On the cross-sectional or between-person level, our study revealed that children who experienced more stress than others moved less. Concurrently, on the intensive longitudinal or within-person level, we found that on average, children were more active on days when they experienced heightened stress. Our cross-sectional finding is fully consistent with the literature as most of the studies ($n = 124$) provide evidence that PS debilitates PA, i.e., a negative correlation and thus this result supports Stults-Kolehmainen and Sinha's of a generally negative influence of PS on PA (Stults-Kolehmainen & Sinha, 2014). Concurrently, our within-person finding reveals a reverse association between PS and PA, i.e., a positive correlation. Unfortunately, there are hardly any within-person investigations on the association between PS and PA, especially not in children. However, our finding is in line with Jones et al. who found within 105 adults that repeated real-time ratings of stress timely coincided with increased accelerometer-measured physical activity (Jones, Taylor, Liao, Intille, & Dunton, 2017) and with results from Buman et al. showing heightened leisure-time exercise on days when young adults ($n = 54$) perceived more stress (Buman et al., 2007). Moreover, Olive, Telford, Byrne, Abhayaratna, and Telford (2016) found a significant between-person effect in boys and girls, showing that more stress was related with less PA, but no longitudinal within-person effects of PS on PA. In a similar vein, we could show in own prior investigations that increased momentary feelings of tension, which may be labeled as emotional counterparts of PS, were associated with heightened physical activity in adolescent's (Koch et al., 2018), adults (Kanning, Ebner-Priemer, & Schlicht, 2015; Reichert et al., 2016; Reichert et al., 2017), and elderly (Kanning et al., 2015).

The underlying biobehavioral mechanisms will have to be researched more closely in future studies to inform tailored treatments. Given our results, one may be tempted to speculate that a positive within-subject association of PS and PA results from children being exposed to multiple stressors in everyday life, such as many appointments on one single day (e.g., a long school day plus leisure time appointments such as music lessons), being physiologically activated multiple times to fulfill the tasks and change locations, which may result in increased PA. In a similar vein, one may be tempted to speculate that a negative between-subject association of PS and PA concurs with the evidence that chronic stress can result in depleted resources due to the costs of physiological arousal. Children have been discussed to be especially vulnerable for negative consequences of this mechanism (Johnston-Brooks, Lewis, Evans, & Whalen, 1998).

Although our study is one of the first ones to tackle the PS–PA association and comes with limitations (see below) that hinder us from providing strong evidence that could guide future intervention approaches, the question arises which conclusions could be derived from different PS–PA associations on the within- and between-subject level. Given that PS comes with detrimental yet PA with beneficial health effects in humans (Chaddock-Heyman et al., 2014; Gomes et al., 2017; Hills et al., 2011; Lagraauw et al., 2015), the positive PS–PA relationship on the within-subject level may call for interventions which treat feelings of distress in children despite impairing their heightened PA levels in stressful situations. Such interventions could draw from latest digital progress using wearables tracking PA and micro-EMA approaches concurrently giving insights into children's stress experiences as recently implemented by Wang et al. (2022). Drawing from ecological momentary interventions (Reichert et al., 2020b), these devices could trigger stress reducing exercises on the children's smartphones in the place needed and just at the moment when treatment is most efficient. Nowadays, huge progress in digital technologies may also help to track both PS and PA on the long run therewith focusing the negative between-subject relationship of PS and PA in children. For example, child-friendly designed fitness watches could track physiological indicators of PS via fine-grained heart rate monitoring and PA via accelerometer across relatively long time periods (Kelly et al., 2007). These devices may help to identify tipping points (Van De Leemput et al., 2014) of children slipping into a phase of chronic stress accompanied by decreased levels of PA, which would be a first step towards preventing depleted physical resources as a result of chronic stress. Moreover, investigations combining ecological valid ambulatory assessment approaches with laboratory neuroimaging (e.g., Reichert et al., 2020a) may not only yield insights on a neurobiological level, but such studies may also inform treatment approaches on who benefits most from interventions on either PA or PS.

This work comes with several limitations which should be tackled in future studies. First, our observational study design in the everyday life of children did not allow for experimental control of third variables. Therefore, since potentially hidden third variables or mechanisms influencing both PS and PA could have been missed, this study design does not allow to draw any causal conclusion (Susser, 1991). We only can evidence associations of PS and PA, but not whether PS did causally impact PA versus whether children experienced altered PS as a consequence of PA. To progress towards ecological valid yet causal findings, e.g., the integration of experimental manipulation into everyday life is warranted (Reininghaus, Depp, & Myin-Germeys, 2016). Especially within person encouragement designs may be suited to tackle those accounts (Schmiedek & Neubauer, 2020). This poses a critical next step for in-depth insights on the PS–PA associations and for the development of ecological momentary interventions (Myin-Germeys, Klippel, Steinhart, & Reininghaus, 2016). Second, the sampling frequency in our study was limited (i.e., one PS questionnaire rating per day). Since the sampling frequency should match the process of interest as good as possible to receive univocal results (e.g., Reichert et al., 2020b), more fine-grained studies taking advantage of the most recent sampling techniques such as electronic diaries on smartphones, or even of latest approaches such as micro-EMA assessments (Ponnada et al., 2022), are warranted to replicate and extend our findings on the association of PS and PA in children. Third, while we received a significant association between PS and PA with the given $n = 74$ on the between-person level, it should be noted that future studies may aim for a larger sample sizes, especially against the background of sampling-related instability of P values; for a more detailed discussion see, e.g., Cumming (2008).

In summary, our expectation to receive more unambiguous insights in the association between PS and PA by clearly differentiating the level of analyses was met by our results that show distinct effects on each analyses level (a negative vs. a positive correlation), which are supported by the respective literature (between-person vs. within-person studies). One may speculate that this points towards distinct directions of the association between PS and PA as a function of the level of analyses. We submit that our finding sheds light on one important aspect when investigating the association between PS and PA. This issue had already been discussed and proved in several other research contexts (Kamarck et al., 2003; Robinson, 2009; Zawadzki et al., 2017). Cross-sectional studies cannot be used as a substitute to investigate within-subject processes; cross-sectional data is not merely a poor proxy for a within-subject associations, these effects are entirely independent. Thus, we emphasize that the level of analyses is highly crucial to receive more unequivocal results. When we are interested in within-person effects of PS on PA, a so far seriously neglected issue, we should ensure we are utilizing, e.g., intensive longitudinal data techniques. In future studies, our specific findings on the PS–PA association should be replicated by assessments and analyses on a more fine-grained sampling scale to proceed towards individually tailored prevention and intervention strategies, e.g., including treatment of children's distress feelings despite impairing their heightened PA levels in stressful situations, and to identify tipping points of chronic stress phases in children via digital solutions such as ecological momentary interventions.

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Funding. Dr. Tost acknowledges grant support by the German Research Foundation (GRK 2350/1 project B2, Collaborative Research Center TRR 265 project A04, Collaborative Research Center SFB 1158 project B04, grant TO 539/3-1) and German Federal Ministry of Education and Research (grant 01EF1803A project WP3). Additional support was received from the Ministry of Science, Research and the Arts of the State of Baden-Wuerttemberg, Germany (grant 42-5400/136/1). Dr. Meyer-Lindenberg acknowledges grant support by the German Research Foundation, Research Training Group GRK2350/1 (project B02), Collaborative Research Center 1158 project B09 and Collaborative Research Center TRR 265 project S02. Additional support was received from the Ministry of Science, Research and the Arts of the State of Baden-Wuerttemberg, Germany (grants 42-5400/136/1 and 42-04HV.MED(16)/16/1), the German Federal Ministry of Education and Research (grant 01EF1803A). Dr. Ebner-Priemer acknowledges grant support by the German Research Foundation Collaborative Research Center TRR 265 projects A04 and S02. Additional support was received from the German Federal Ministry of Education and Research (grant 01EF1803A).

Author Contribution. AM-L, HT, UE-P, and AZ conceived and designed the study. MR, SB, IR, UB, MG, AH acquired, analyzed and interpreted the data. MR, SB, and UE-P drafted the first version of the manuscript. IR, UB, MG, AH, AZ, AM-L, HT revised it critically for important intellectual content. All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding. Open Access funding enabled and organized by Projekt DEAL.

Declarations

Conflict of interest. UW Ebner-Priemer reports personal fees from Boehringer Ingelheim for consulting outside the submitted work. A Meyer-Lindenberg reports lecture fees from the Lundbeck International Foundation, Paul-Martini-Stiftung, Lilly Deutschland, Atheneum, Fama Public Relations, IDIBAPS, Janssen-Cilag, Hertie-Stiftung, Bodelschwingh-Klinik, Pfizer, Universität Freiburg, Schizophrenia Academy, Hong Kong Society of Biological Psychiatry, Spanish Society of Psychiatry, Italian Society of Biological Psychiatry, Reunions I Ciencia S.L. Brain Center Rudolf Magnus UMC Utrecht, Friedrich-Merz-Stiftung, and consultant fees from Boehringer Ingelheim, Elsevier, Brainsway, Lundbeck Int. Neuroscience Foundation, Lundbeck A/S, Sumitomo Dainippon Pharma Co., Academic Medical Center of the University of Amsterdam, Synapsis Foundation-Alzheimer Research Switzerland, IBS Center for Synaptic Brain Dysfunction, Blueprint Partnership, University of Cambridge, Deutsches Zentrum für Neurodegenerative Erkrankungen, Zürich University, Brain Mind Institute, L.E.K. Consulting, ICARE Schizophrenia, Science Advances, Fondation FondaMental, von Behring Röntgen Stiftung, The Wolfson Foundation, Sage Therapeutics outside the submitted work. M. Reichert, S. Brüßler, I. Reinhard, U. Braun, M. Giurgiu, A. Hoell, A. Zipf and H. Tost declare that they have no competing interests.

Our study was approved by the Medical Ethics Committee of Heidelberg University, Germany. Parents gave written informed consent for their children, who received monetary compensation for their effort.

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