Editorial Commentary

On the road to exercise as medicine for depressive symptoms in young people

Arnaud Philippot[1,2,3]^, Yannick Bleyenheuft[3], Vincent Dubois[1], Juan Martin Tecco[4], Tine Van Damme[2], Davy Vancampfort[2]

[1]AREA+ Psychiatric Units for Adolescents, Epsylon ASBL Psychiatric Network, Brussels, Belgium; [2]Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium; [3]Institute of Neurosciences, UCLouvain, Louvain-La-Neuve, Belgium; [4]Department of Psychiatry, Centre Hospitalier Universitaire et Psychiatrique de Mons-Borinage (CHUP-MB), Mons, Belgium

Correspondence to: Arnaud Philippot, PhD. AREA+ Psychiatric Units for Adolescents, Epsylon ASBL Psychiatric Network, Brussels, Belgium; Institute of Neurosciences, UCLouvain, Louvain-La-Neuve, Belgium; Department of Rehabilitation Sciences, KU Leuven, Tervuursevest 101, Box 1501, 3001 Leuven, Belgium. Email: Arnaud.philippot@kuleuven.be.

Comment on: Recchia F, Bernal JDK, Fong DY, *et al.* Physical Activity Interventions to Alleviate Depressive Symptoms in Children and Adolescents: A Systematic Review and Meta-analysis. JAMA Pediatr 2023;177:132-40.

Keywords: Exercise; depressive symptoms; children; adolescents

Submitted Apr 20, 2024. Accepted for publication Jul 09, 2024. Published online Jul 29, 2024.
doi: 10.21037/tp-24-152
View this article at: https://dx.doi.org/10.21037/tp-24-152

Worldwide increasing rates of depression have brought considerable global health challenges, for which further prevention and treatment countermeasures are urgently needed (1). More in detail, between 1990 and 2019, the global prevalence of major depression increased with 10.2% in children and adolescents (<20 years) resulting in an age-standardized rate of 693.5 per 100,000 in 2019 (1). Clinical practice guidelines for preventing and treating depression in children and adolescents typically include psychotherapy, specifically cognitive-behavioral and interpersonal therapies, and selective serotonin reuptake inhibitor medication (2). The potential of exercise, i.e., planned, structured, and repetitive physical activity with a final or intermediate objective to improve or maintain health outcomes (3), which is nowadays considered a first-line treatment for mild to moderate depression and a complementary treatment for major depression in adults and elderly, is neglected in this younger age group (4). One of the reasons could be that the scientific evidence was insufficiently systematically and rigorously summarized. Recchia *et al.* (5) addressed this knowledge gap and performed a well-written systematic review and meta-analysis examining the effect of exercise on the reduction of depressive symptoms in children and adolescents. The authors demonstrated that exercise significantly alleviates symptoms of depression compared to control conditions, although the effect was small [g=−0.29; 95% confidence interval (CI): −0.47 to −0.10; P=0.004]. Findings were based on 21 studies involving 2,441 participants [1,148 (47.0%) boys; 1,293 (53.0%) girls]. The mean [standard deviation] age of participants was 14 [3] years to a maximum of 18 year. In secondary analyses, the authors did find a moderate effect, showing a reduction in co-morbid depressive symptoms in children and adolescents with a mental illness (e.g., attention deficit hyperactivity disorder) and a reduction in core symptoms in those with major depressive disorder (n=6, g=−0.74, 95% CI: −1.01 to −0.47), while the effect was negligible for healthy participants (n=9, g=−0.09, 95% CI: −0.18 to 0.00).

What do these general findings teach us?

First, the data of Recchia *et al.* (5) are in line with previous meta-analyses (6-8) and justify the use of exercise as

^ ORCID: 0000-0002-0706-4491.

a complementary treatment modality for depressive symptoms in young people. More research comparing exercise directly with active control conditions such as pharmacotherapy and/or psychotherapy in those with a clinical depression is however needed before deciding whether exercise should also be considered as a first-line treatment. A very recent randomized controlled trial in adults with clinical depression and/or anxiety did investigate the mental and physical health effects of 16 weeks of running therapy versus pharmacotherapy and demonstrated that there was no difference in remission rates between both conditions, while running outperformed pharmacotherapy in terms of physical benefits (9).

Second, while the meta-analysis by Recchia *et al.* (5) shows a moderate effect for (I) a reduction in co-morbid depressive symptoms in adolescents with a mental illness, and (II) a reduction in core symptoms in those with a clinical diagnosis of depression, a negligible antidepressant effect was found in healthy children and adolescents. This lack of significant reduction in healthy children and adolescents could be explained by a flooring effect. From a public health perspective, it is however advised as well to recommend young people without depressive symptoms to be physically active in order to strengthen their resilience and reduce the risk for depression (10). A previous meta-analysis already demonstrated that self-reported physical activity protects against the emergence of self-reported depression in youth (adjusted odds ratio =0.90, 95% CI: 0.83 to 0.98) (11), while recent cohort studies using objectively measured physical activity in children and adolescents with a clinical depression showed similar preventative effects (12,13).

Although lessons can be learnt from the meta-analysis, some findings need to be interpreted with caution.

First, Recchia *et al.* (5) conducted an exploratory analysis investigating differences in exercise effects between children aged <13 years, and adolescents aged ≥13 years and found greater beneficial effects for adolescents (g=–0.44, 95% CI: –70 to –0.19) compared to children (g=–0.05, 95% CI: –0.18 to 0.09). The authors concluded that the effect of exercise may be different at different ages. Recchia *et al.* (5) used the cut-off of 13 years as physical activity levels start to decline at this age. While it is relevant to investigate effects in narrower age groups, we should be very careful in interpreting the results of Recchia *et al.* (5). A reason is that the prevalence of depression is different across developmental stages, e.g., between the age of 5 to 9, the age of 10 to 14 (early adolescence) and above 15 years (late adolescence) and studying exercise in specific developmental stages seems to be relevant (14). Another reason to be cautious in interprating the age-related findings of Recchia *et al.* (5) is that only 2 of the 8 trials involving children aged <13 years included children with mental illness and the other 6 were perfomed in healthy participants. Consequently, there is also a high risk for a flooring effect in children aged <13 years which reduces the reliability of the results.

Second, Recchia *et al.* (5) provided specific practical recommendations for exercise interventions, i.e., FITT principles (frequency, intensity, type and time). For example, with regards to the frequency, Recchia *et al.* (5) concluded that being physically active three times per week leads to greater benefits than two or less times. No recommendations were however formulated related to the intensity or the time/duration of a single exercise session. How exercise intensity was defined was moreover absent in the current meta-analysis. This lack of clarity prevents us from drawing any firm clinical conclusions. With regards to the type of exercise, Recchia *et al.* (5) focused on aerobic exercise. Not exploring other types of structured exercise, such as resistance training, was a missed opportunity. A very recent meta-analysis exploring the evidence between different exercise types in children and adolescents demonstrated that aerobic exercise had the largest effect on reducing depressive symptoms, followed by resistance exercise training (15). The latter meta-analysis teaches us as well that children and adolescents should be offered different choices when trying to motivate them to exercise. It is well established that when young people with mental illness enjoy the exercise they are doing, they are also more likely to remain exercising over a longer period of time (16,17). Since Recchia *et al.* (5) did, in fact, not focus on exercise but rather on physical activity, i.e., "any bodily movement produced by skeletal muscles that requires energy expenditure", it was also a missed opportunity to investigate the physical activity domain (e.g., leisure time physical activity, school-based physical activity, active commuting) in more detail (18). Such differentiation is essential. As demonstrated in a previous meta-analysis in adolescents and adults, the mental health benefits of physical activity might differ between domains with more beneficial effects observed during leisure time and for actively commuting, while no benefits are observed for physical education (19).-

Finally, analyses can only be as good as the available evidence from individual trials. Recchia *et al.* (5) were not

able to perform several exploratory analyses due to a lack of data, e.g., related to participants' characteristics and type of supervision provided. Therefore, future exercise trials need to report accurately the FITT characteristics, whether exercise was provided in group or not, in nature or in/outdoors, the type of peer-provider interaction, quality of supervision, adherence, dropout rates and reasons for dropout. A previous meta-analysis investigating dropout from exercise in adults with depression demonstrated that supervision by an expert such as a physiotherapist results in less dropout (20). In addition, a more detailed description of the participants themselves is needed: use of standardized and preferably objective measures (21) for actual physical activity participation pre- but also post-intervention, physical activity history, actual physical fitness levels, severity of depression, acute or chronic depression, mental and physical co-morbidities, prescription of medication and family history of mental health. These data would make it possible to explore which interventions would work best for which subgroups.

In summary, the meta-analysis of Recchia *et al.* (5) provides a rationale for the inclusion of exercise as medicine within multi-disciplinary treatment programs aiming to alleviate co-morbid depressive symptoms in adolescents with mental illness and core symptoms in those with a clinical diagnosis of major depressive disorder. Some caution is however needed when interpreting the results. Considering the recent rise in meta-analyses being published, such as the one of Recchia *et al.* (5), the authors do believe the time is now to translate this evidence into real-world initiatives. Future studies evaluating the effectiveness of exercise interventions for children and adolescents with depression in real-world settings will help to understand how to "make a program work" in routine clinical practice (22,23). In this context, understanding engagement barriers and facilitators at individual (e.g., social determinants, physical and mental co-morbidities, etc.), system (e.g., access to facilities, quality of the supervision) and policy (e.g., reimbursement schemes) levels is crucial. Addressing this research gap necessitates the creation of a comprehensive framework that can guide the development and implementation of engaging, effective, and scalable exercise programs. This framework can build upon the work of Recchia *et al.* (5).

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Pediatrics*. The article has undergone external peer review.

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-152/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-152/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

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Cite this article as: Philippot A, Bleyenheuft Y, Dubois V, Tecco JM, Van Damme T, Vancampfort D. On the road to exercise as medicine for depressive symptoms in young people. Transl Pediatr 2024;13(7):1279-1282. doi: 10.21037/tp-24-152