might ignore crucial clinical issues such as safety, patient preference, and cost-effectiveness.1 It is obvious that the evaluation of safety in this article was not sufficient, because some important adverse effects such as sleep disturbance, headache, and loss of appetite were not mentioned. Moreover, the authors concluded that methylphenidate was the first pharmacological choice for ADHD in children and adolescents; however, stimulants (such as methylphenidate) are contraindicated in patients with psychosis, hypertension, or tics because these conditions can be exacerbated by these medications. This contraindication should be explained to avoid misleading in the article.3

In summary, Samuele Cortese and colleagues made an effort to compare ADHD medications in terms of efficacy and tolerability. Their findings are likely to have a substantial effect on clinical practice guidelines. Although the findings of their analysis are undoubtedly important, the results should be considered within a wider clinical context, including side-effects and comorbidity.

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To justify the trend for prescribing attention deficit hyperactivity disorder (ADHD) drugs requires a detailed risk-benefit analysis. The statistical approach of meta-analysis used by Samuele Cortese and colleagues1 gives support to the efficacy of ADHD medication. However, their meta-analysis provides little reassurance of safety. Tolerability, cited as a reassuring measure of safety, is a limited endpoint. Tolerability to heroin does not confirm its safety, and tolerability to homeopathic remedies does not confirm their efficacy.

Both the diagnosis and the primary measures of efficacy in psychiatry rely on changes in symptoms compounded into score-based rating scales. Individual symptoms alone are not powerful enough for change to be detected. Adverse events are not grouped in this way, so the safety analysis does not match the power of the efficacy composite endpoint.1 This imbalance is analogous to detecting efficacy with a microscope and safety with a passing glance. On a rare occasion where psychiatry used a sensitive composite endpoint for safety, the Columbia-Suicide Severity Rating Scale, a range of drug labels were updated to reflect previously undetected safety concerns.2 Adverse events for any ADHD drug include central and peripheral symptoms that could easily be compiled into a composite endpoint to reflect their unwanted sympathomimetic activity.1 Safety concerns about amphetamines, or amphetamine-like drugs—often now used for ADHD—were discovered in the 1940s and 1950s.

Starting so many children on a potential lifetime of amphetamine-type drug use is relatively new in the UK, copying practice in the USA. The use of composite endpoints on only one side of the risk-benefit equation to justify this is not evidence-based medicine.2


Authors’ reply
We agree with Erlend Faltinsen and colleagues that standardised mean differences can be difficult to translate into clinical practice. As reported in the Cochrane handbook, the mean difference (or more correctly, difference in means) measures the absolute difference between the mean value in two groups and then estimates the average amount that the experimental intervention changes in the outcome compared with that of the control intervention. Mean difference can be used in meta-analysis as a summary statistic only when outcome measurements in all studies are made on the same scale. By contrast with standardised mean differences, the overall intervention effect can be difficult to interpret because it is reported in units of SD rather than in units of a specific rating scale. Although, in some circumstances, it is possible to transform the effect back to the units used in a specific study, the problem with standardised mean differences is that this method assumes that differences in SD between studies reflect differences in measurement scales and not real differences in variability among study populations.

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This information about tolerability will complete the clinical picture of the safety profile of ADHD medications and will better inform patients, carers, clinicians, and treatment guidelines. SC declares reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for CAMH, and from Healthcare Convention for educational activity on ADHD. NA declares travel support to attend a conference by Shire. TB declares advisory or consultancy roles for Actelion, Hexal Pharma, Eli Lilly, Medice, Novartis, Oxford Outcomes, Otsuka, PDM Scientific, Shire, and Viforpharma; conference support or speaker’s fees from Medice, Novartis, and Shire; royalties from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press; and is involved in clinical trials undertaken by Shire and Viforpharma. DC declares grants and personal fees from Shire and Servier; personal fees from Eli Lilly, Novartis, and Oxford University Press; and grants from Vifor. CH is supported by the National Institute of Health Research (NIHR) Nottingham Biomedical Research Centre and the NIHR MindTech MedTech Co-operative. CH and ES are members of the National Institute for Health and Care Excellence (NICE) ADHD Guideline Group. AZ declares honoraria for participating in Advisory boards or Data Safety Monitoring Boards for Eli Lilly, Otsuka, Lundbeck, Takeda, and EdusPharma; royalties from Oxford University Press and Gruen US; and research grants from Lundbeck, Roche, Shire, and Vifor. AC is supported by the NIHR Oxford Cognitive Health Clinical Research Facility. CDG declares no competing interests.

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the cross-sectional observation that individuals reporting the highest levels of exercise also reported poorer mental health. Troublingly, this has been interpreted as high levels of exercise (ie, more than 6 h per week, or about 52 min per day) having adverse effects on mental health. This cannot be asserted from the data, for multiple reasons. First, the cross-sectional nature of the study introduces high chance of reverse causation. People who have frequent stress or depression might engage in daily exercise to counter such conditions, especially because exercise is a publicly accepted self-management strategy for mental illness. By analogy, engaging in highly frequent psychotherapy, or taking higher doses of antidepressant medication, could also be cross-sectionally associated with poor mental health—but this should not be misinterpreted as worsening mental health.

Second, self-reported measures are notoriously poor at capturing actual physical activity, even in the general population. Furthermore, population-scale data\(^4\) published in 2017, from the UK Biobank, have shown that individuals with severe mental illness overestimate their physical activity in comparison with the general population. Therefore, the observation by Chekroud and colleagues that individuals with poorest mental health reported the highest physical activity could be partly attributable to the known overreporting of physical activity in this population.

Finally, the implied adverse effects from this cross-sectional analysis are unsupported by experimental data, because there is no evidence of negative psychological effects from high doses of exercise in randomised trials. Indeed, in contrast to these cross-sectional indications, 90-min bouts of vigorous exercise have been shown to produce positive neurobiological responses,\(^5\) activating the endocannabinoid system and upregulating brain-derived neurotrophic factor, the two neurochemical factors attributable for the antidepressant benefits of exercise.\(^5\)

Therefore, it is at least premature—and at worst harmful and dangerous—for conventional or social media to disseminate information that a daily hour of exercise might impede mental wellbeing. The obvious casual limitations of the findings by Chekroud and colleagues should be seriously considered, alongside our comments in this Correspondence, to prevent researchers, clinicians, and the public from prematurely concluding that daily exercise reduces mental health.

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