might ignore crucial clinical issues such as safety, patient preference, and cost-effectiveness.[3] 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.[4] 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.[5]

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.

We declare no competing interests.

*Shuai Wang, *Yi Zheng*
yizheng@ccmu.edu.cn

Beijing Anding Hospital, Capital Medical University and Institute for Brain Disorders, National Clinical Research Center for Mental Disorders, Beijing, 100001, China

1 Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2018; **5:** 727–38.
2 Lin DY, Kratochvil CJ, Xu W, et al. A randomized trial of edivoxetine in pediatric patients with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2014; **24:** 190–200.
3 Volkow ND, Swanson JM. Clinical practice: adult attention deficit-hyperactivity disorder. *N Engl J Med* 2013; **369:** 1935–44.
4 Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet* 2016; **387:** 1240–50.
5 Santosh P. Stimulant medication to treat attention-deficit/hyperactivity disorder. *BMJ* 2017; **358:** j2945.

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 colleagues[1] 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.[2] 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.[3] 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.[2] 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]

I report personal dividends from Medicines Assessment, outside the submitted work; I am Executive Editor of the British Journal of Clinical Pharmacology; I am a member of the Joint Speciality Committee for Clinical Pharmacology and Therapeutics at the Royal College of Physicians, and I have acted as representative of the Royal College of Physicians at the All Party Parliamentary Group for Prescribed Drug Dependence.

John B Warren
jbwarren5@gmail.com

London SE16 7RB, UK

1 Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2018; **5:** 727–38.
2 Warren JB. Composite endpoints and the distortion of risk benefit analysis. *Brit J Clin Pharmacol* 2017; **83:** 221–23.
3 US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry. Suicidal ideation and behavior: prospective assessment of occurrence in clinical trials. 2012. https://www.fda.gov/downloads/drugs/guidances/ucm225130.pdf (accessed Aug 17, 2018).

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. This assumption could be problematic in circumstances in which there might be real differences in variability between the participants in different studies (for instance, pragmatic *vs* explanatory studies). For this reason, we paid careful attention when we drafted the inclusion and exclusion criteria in the protocol of our review[1,2] and selected only trials that were similar in design, population, and interventions to reduce heterogeneity and inconsistency.[3] This selection led to the inevitable exclusion of several trials. Even though we did an extensive search for published and unpublished data and contacted all study authors and pharmaceutical companies for additional data, we might, as is typically the case in systematic reviews, have missed some relevant studies. However, we do not agree that we should have included all the studies in the 2015 Cochrane review.[4] Before finalising our list of included studies, we screened existing systematic reviews for any relevant reference in their lists of included (and excluded) studies. As detailed in the appendix of our review, we had to exclude several studies that were included by Ole Jakob Storebø and colleagues:[4] 51 studies with less than 7 days of treatment, 38 crossover studies without wash-out period and no pre-crossover data (even after contacting the authors), 18 studies in which patients were responders to previous treatment, 14 studies where treatment was not as monotherapy, and a range of other studies without appropriate randomisation, with single-blind design, that included preschool children, or that administered non-oral formulation of the investigational drug. Including these trials would have been a clear violation of our published protocol and a material risk for the transitivity of the network.[3]

As prespecified in our peer-reviewed protocol,[1,2] tolerability (proportion of patients who dropped out of studies because of side-effects) was chosen as primary outcome because it is consistently reported across studies and it is a hard outcome used in other similar reviews.[5] We also analysed all-cause discontinuation as a pre-defined secondary outcome. It is an important measure of treatment acceptability and full results are reported in the main text of our review and in the online appendix.

We did not include edivoxetine because, when we drafted the protocol, we focused only on the drugs that were licensed or mentioned in international clinical guidelines at the time. We agree with Shuai Wang and Yi Zheng that systematic reviews should be as comprehensive as possible. We are aware that many new drugs for attention deficit hyperactivity disorder (ADHD) will be on the market in the near future. As we did with another network meta-analysis,[6] we plan to publish the update of this review in a few years' time and will include in the network, as appropriate, all the relevant medications that will be available at that time.

In our network meta-analysis, we summarised the best available evidence about efficacy and acceptability of ADHD medications. In the protocol, we planned analyses of clinical outcomes at different time-points (acute and long term) but, unfortunately, there are not enough randomised controlled trials in the field. More long-term data and higher quality studies are urgently needed. We totally agree with John Warren that it is important to consider reliable information also about safety and harms when choosing a pharmacological treatment for ADHD (of course, this applies to any intervention in any disorder in any field of medicine). We are working on this question and have almost completed the data collection for a parallel project (based on the same protocol), which investigates the profile of specific adverse events for each drug, including—among others—psychotic symptoms, suicidality, sleep problems, headache, loss of appetite, and tics. 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, PCM 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 Monitory Boards for Eli Lilly, Otsuka, Lundbeck, Takeda, and EduPharma; royalties from Oxford University Press and Giunti OS; 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.

**Andrea Cipriani, Nicoletta Adamo, Cinzia Del Giovane, David Coghill, Tobias Banaschewski, Chris Hollis, Alessandro Zuddas, Emily Simonoff, Samuele Cortese*

andrea.cipriani@psych.ox.ac.uk

Department of Psychiatry, University of Oxford, and Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford OX3 7JX, UK (AC); Department of Child and Adolescent Psychiatry, King's College London, and Institute of Psychiatry, Psychology and Neuroscience, and National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre, London, UK (NA, ES); Statistics and Methodology, Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland (CDG); Departments of Paediatrics and Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, VIC, Australia (DC); Division of Neuroscience, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK (DC); Murdoch Childrens' Research Institute, Melbourne, VIC, Australia (DC); Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim and University of Heidelberg, Mannheim, Germany (TB); Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK (CH, SC); NIHR MindTech MedTech and In-vitro Diagnostic

Cooperative, and Centre for ADHD and Neurodevelopmental Disorders Across the Lifespan (CANDAL), Institute of Mental Health, University of Nottingham, Nottingham, UK (CH); Child and Adolescent Neuropsychiatry Unit, Department of Biomedical Sciences, University of Cagliari and "A Cao" Paediatric Hospital, Cagliari, Italy (AZ); Centre for Innovation in Mental Health, Academic Unit of Psychology, and Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK (SC); Solent NHS Trust, Southampton, UK (SC); and New York University Child Study Center, New York, NY, USA (SC)

1 Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2018; **5:** 727–38.

2 Cortese S, Adamo N, Mohr-Jensen C, et al. Comparative efficacy and tolerability of pharmacological interventions for attention-deficit/hyperactivity disorder in children, adolescents and adults: protocol for a systematic review and network meta-analysis. *BMJ Open* 2017; **7:** e013967.

3 Mavridis D, Giannatsi M, Cipriani A, Salanti G. A primer on network meta-analysis with emphasis on mental health. *Evid Based Ment Health* 2015; **18:** 40–46.

4 Storebø OJ, Ramstad E, Krogh HB, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev* 2015; **11:** CD009885.

5 Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016; **388:** 881–90.

6 Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018; **391:** 1357–66.

Physical activity and mental health

In *The Lancet Psychiatry*, Chekroud and colleagues[1] presented a large cross-sectional examination of physical activity and mental health. Despite imprecision about the terms mental health and exercise in the study—and the cross-sectional design—the findings overall match the existing body of longitudinal research showing that regular physical activity is associated with better mental health.[2]

Although the article has received extensive media coverage, much of this has unfortunately focused on 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.[3] 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.

We declare no competing interests. BS is supported by Health Education England and the National Institute for Health Research (NIHR) HEE/NIHR ICA Programme Clinical Lectureship (ICA-CL-2017-03-001). BS is also partly supported by the Maudsley Charity and the NIHR Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust. JF is supported by a Blackmores Institute Fellowship.

**Brendon Stubbs, Davy Vancampfort, Lee Smith, Simon Rosenbaum, Felipe Schuch, Joseph Firth*
brendon.stubbs@kcl.ac.uk

Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK (BS); South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, UK (BS); Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium (DV); University Psychiatric Center, KU Leuven, Kortenberg, Belgium (DV); Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK (LS); (SB); (SB); (FS); (JF); (JF); and UK (JF)

1 Chekroud SR, Gueorguieva R, Zheutlin AB, et al. Association between physical exercise and mental health in 1·2 million individuals in the USA between 2011 and 2015: a cross-sectional study. *Lancet Psychiatry* 2018; **5:** 736–46.

2 Schuch FB, Vancampfort D, Firth J, et al. Physical activity and incident depression: a meta-analysis of prospective cohort studies. *Am J Psychiatry* 2018; **175:** 631–48.

3 Jorm AF, Korten AE, Jacomb PA, et al. Helpfulness of interventions for mental disorders: beliefs of health professionals compared with the general public. *Br J Psychiatry* 1997; **171:** 233–37.

4 Firth J, Stubbs B, Vancampfort D, et al. The validity and value of self-reported physical activity and accelerometry in people with schizophrenia: a population-scale study of the UK Biobank. *Schizophr Bull* 2017; published online Oct 24. DOI:10.1093/schbul/sbx149.

5 Heyman E, Gamelin F-X, Goekint M, et al. Intense exercise increases circulating endocannabinoid and BDNF levels in humans—possible implications for reward and depression. *Psychoneuroendocrinology* 2012; **37:** 844–51.

Published **Online** September 20, 2018 http://dx.doi.org/10.1016/S2215-0366(18)30343-2