


In Reply We appreciate the opportunity to respond to the letter about our study on maternal prescriptions filled for antipsychotics during pregnancy and offsprings’ school performance. Dr Jingjing and colleagues suggest the implementation of propensity score matching over multivariable regression to balance the covariates.

Propensity score matching is commonly used for control of confounding in pharmacoepidemiologic studies, especially when the outcomes are rare, many confounders are present, and there are systematic differences in the distribution of characteristics between groups. In the present study, outcomes were standardized test scores in language and mathematics (continuous variables), and our sample was sufficiently large to allow for the inclusion of all a priori identified confounders without overfitting the models. In this scenario, the propensity score approach would yield similar or slightly weaker associations to the traditional multivariable regression and would reduce precision and statistical power due to nonmatched observations being discarded. Furthermore, our conclusions across all 7 sensitivity analyses were consistent, including analyses of better-balanced populations (eg, sibling comparisons and children of mothers with antipsychotic prescription fills before vs during pregnancy).

In addition, Dr Jingjing and colleagues remarked on the potential confounding by prepregnancy body mass index (BMI). Our thoughts are the following. Individuals who are overweight and obese are at higher risk of developing mental illnesses. Therefore, prepregnancy BMI could potentially be associated with the likelihood of receiving antipsychotic treatment during pregnancy. Our study was based on the linkages of Danish nationwide registers, and information on prepregnancy BMI was not included in the Danish Medical Birth Registry until 2003. We acknowledged potential residual confounding from any unmeasured factors in our discussion. However, we considered other covariates, eg, maternal age, smoking, and education, which would partly control for prepregnancy BMI, and we expect that further adjustment for prepregnancy BMI would not change the results substantially. To test this assumption, we conducted a subgroup analysis restricted to 296 306 children born from 2004 to 2009. In this additional analysis of 565 671 language tests and 329 328 mathematics tests, we found that maternal prescription fill for antipsychotics was not associated with test score performance in language (adjusted difference, 0.5 [95% CI, −1.3 to 2.2]) and further adjustment for prepregnancy BMI, 0.7 [95% CI, −1.0 to 2.4]) or in mathematics (adjusted difference, 0.7 [95% CI, −1.4 to 2.7]) and further adjustment for prepregnancy BMI, 0.9 [95% CI, −1.2 to 2.9]). These results completely align with our findings in the primary analyses in the full population (children born in 1997–2009, adjusted difference, 0.5 [95% CI, −0.8 to 1.7] for language and 0.4; [95% CI, −1.0 to 1.8] for mathematics). Therefore, further adjustment for prepregnancy BMI did not change the overall conclusion of the study; that is, maternal antipsychotic prescription during pregnancy did not appear to be associated with offspring standardized test scores.

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Is There a Role for Thromboprophylaxis in Selected Outpatients With COVID-19?

To the Editor Mr Xie and colleagues provide important information on an understudied topic: incident venous thromboembolism (VTE) in outpatients with COVID-19. The findings of their study are commendable and provide useful conclusions. First, COVID-19 was associated with increased VTE risk, even in the outpatient setting given that a higher VTE incidence was shown among 18 818 outpatients with COVID-19 compared with 93 179 propensity score matched, noninfected participants. Second, patients with specific characteristics (older age, male sex, obesity, no/partial vaccination, and inherited thrombophilia) had higher VTE risk. Third, the VTE risk was high for up to 30 days after diagnosis. These findings are highly important and may advance case management and treatment for outpatients with COVID-19.

At present, the available data are generally against the routine use of pharmacologic thromboprophylaxis in outpatients with COVID-19. Moreover, current guidelines do not provide specific recommendations. However, it is common sense that selected outpatients with VTE risk factors are therefore at higher risk for disease worsening and would benefit from
thromboprophylaxis on an individualized basis and after careful assessment of bleeding risk. Indeed, data show that major adverse events tend to occur early in patients hospitalized with COVID-19 who have a high-risk profile; prompt thromboprophylaxis would benefit these patients. 5

The study by Mr Xie and colleagues1 was performed during a period when only 41% of patients with COVID-19 had been fully vaccinated; a percentage that has increased worldwide. Thus, it would be interesting to study VTE risk factors separately among the fully vaccinated group—despite VTE events having been infrequent. Moreover, apart from the patient risk factors, the disease characteristics may play a role. Symptoms that indicate disease activity or severity, ie, the duration of the fever, could be contributing to an increased VTE risk in selected patients. In addition, SARS-CoV-2 variants may exhibit a different risk regarding VTE. If these data are available, they would make for another interesting study.

Although thromboprophylaxis among outpatients with COVID-19 is not generally recommended, the data and findings derived from studies, such as this one by Mr Xie and colleagues,1 show that selected outpatients carry an increased VTE risk. On the other hand, widespread immunization, as well as the availability of the antiviral therapies, may be substantially reducing VTE risk. Whether thromboprophylaxis would benefit high-risk outpatients with COVID-19 is unclear, but it seems reasonable to conclude that an individualized strategy would improve their prognosis.

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In Reply In our recent research article regarding clinical and genetic determinants associated with venous thromboembolism (VTE) among community-dwelling patients with COVID-19,1 we reported a marked increase of 30-day VTE and identified older age, male sex, obesity, no or partial vaccination, and inherited thrombophilia as key risk factors. We appreciate the insightful comments from Prof Kollias and colleagues and their support of our call for targeted VTE thromboprophylaxis for outpatients with COVID-19.

Hospitalization is the recommended indicator for initiating antithrombotic therapy for patients with COVID-19. However, we argue that the likelihood of post–COVID-19 VTE should be conceptually seen as a continuum, with some outpatients treated for COVID-19 at an even higher risk of VTE than some hospitalized patients. Also, given that VTE hazard peaks substantially and shortly after SARS-COV-2 infection,2 individuals with COVID-19 would likely benefit from earlier interventions for primary prophylaxis. Our study3 identified several independent risk factors that can be used to stratify patients with different risk profiles for post–COVID-19 VTE. We should highlight that although existing trials (eg, ETHIC, ACTIV-4B) did not generally support routine pharmacologic thromboprophylaxis for outpatients with COVID-19, the results should be interpreted as inconclusive given the great statistical uncertainty and underrepresentation of older patients, and consequently, the low event rates. Therefore, the results do not preclude the use of thromboprophylaxis in selected outpatient subpopulations, particularly among those with a high baseline risk of VTE.3 Further trials targeting high-risk infected outpatients and more real-world studies with larger sample sizes and longer follow-up are warranted to supplement the existing evidence.4

Admittedly, the net benefits of antithrombotic therapy should always be weighed against potential harms5—eg, for those at high risk of VTE, risk of bleeding should be considered when prescribing antithrombotic therapy.6 Of note, genetic risk owing to monogenic thrombophilia or polygenic risk score, as evidenced in our study,1 was exclusively associated with venous but not arterial thromboembolism, which may be promising for identifying individuals susceptible to VTE but resistant to bleeding. Finally, we agree with the proposal from Prof Kollias and colleagues to investigate whether the risk factors persist in fully vaccinated people and what potential value disease symptoms may have for VTE prediction. However, our available data are insufficient for answering this question given the limited sample size: only 6 VTE events among the breakthrough infection cohort.

As the number of COVID-19 outpatient cases continues to increase, personalized prophylactic anticoagulation in this large population may prevent a substantial number of individuals with COVID-19 from developing severe thrombotic complications that require hospitalization and/or intensive care. The clinical and genetic risk factors identified by our study1 should inform the identification of participants for new research to bridge the knowledge gaps on the risk vs benefit of pharmacologic thromboprophylaxis.

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To the Editor We read with great interest the recently published article by Dr del Pozo Cruz and colleagues who reported findings that solidify the reverse dose-response association between daily step counts and mortality incidence. The most pronounced mortality benefits (all cause, cardiovascular, and cancer) in the cohort with a mean (SD) age of 61 (8) years were achieved with approximately 10,000 daily steps (possibly more for cancer) and a peak 30-minute cadence of 70 to 100 steps per minute (spm). These new data constitute recommendations to complement the current physical activity (PA) guidelines, which are primarily formulated as the less readily assessed time engaged in PA. Moreover, data that are step based are more easily tracked by wearable devices. Wearable PA trackers have indeed emerged as valuable tools for improving PA levels and health in users.

To best estimate adherence to PA guidelines, the provision of a conversion key for translating step counts into walking time would be useful. A conversion key would further simplify the comparison of potentially differential outcomes, eg, adherence to step count or walking time targets and health-related consequences.

Translation of optimal step counts (approximately 10,000 steps as reported by Dr del Pozo Cruz colleagues) into corresponding walking times yields approximately 143 minutes or 100 minutes of walking per day (1000 or 700 minutes/week) at a cadence of 70 or 100 smp, respectively. Considering that 70 smp represents light PA (about 2 metabolic equivalents of task (METs)) and 100 smp represents moderate PA (3 METs), the findings by Dr del Pozo Cruz and colleagues are absolutely in line with the outcomes of large prospective cohort studies that have demonstrated maximal reduction of all-cause mortality for approximately 100 minutes of moderate intensity PA per day (700 minutes/week). Moreover, Dr del Pozo Cruz and colleagues confirm that lower amounts of PA are required for maximum reduction of mortality associated with cardiovascular disease than for cancer deaths.

This study by Dr del Pozo Cruz and colleagues is important not only because it confirms previously reported optimal PA levels using an alternative practical measurement approach, but also because it provides a way for interconverting step amounts and PA times. This information may facilitate adherence to PA guidelines and reliance on wearable devices, which have been shown to increase PA levels, thereby contributing to improved public health.

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In Reply We have read with interest the letter from Dr Burtscher and colleagues concerning our recent work, which details the prospective dose-response associations of daily step counts and intensity with cardiovascular and cancer disease incidence and mortality outcomes. We are keen on the idea proposed by Dr Burtscher and colleagues on converting intensity-specific step counts into walking time to further improve the application of step-based targets for better public health.