PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The risk of neuropsychiatric adverse events associated with montelukast use in children and adolescents: a population-based case-crossover study
AUTHORS	Kim, Jae Won Kim, Mideum Seo, Min Sook Shin, Ju-Young

VERSION 1 - REVIEW

REVIEWER NAME	Dr. Bronwyn K. Brew
REVIEWER AFFILIATION	University of New South Wales Sydney United Kingdom of Great Britain and Northern Ireland
REVIEWER CONFLICT OF INTEREST	No
DATE REVIEW RETURNED	14-Feb-2024

GENERAL COMMENTS	Thanks for the opportunity to review this paper. The methods are very thorough. I only have a few thoughts: 1. In the introduction please briefly summarise the limitations/short comings in the studies that have found no association between montelukast and NPAEs to help justify another study. 2. In the methods I don't understand how the wash out period can be 5 days when you can see an effect up to 56 days later after prescription. Perhaps the wash out should be longer? 3. The different hazards windows in Table 2 have the same effect size, I would have expected either a dose response or a maximum effect eg at 4-7 days as others have found with a decrease before and after. Can the authors explain why the effect size would be the same regardless of time? 4. I could not find the Pranlukast results in the results section only in the discussion. I suggest they be moved to the results section with only a comment on interpretation and significance in the discussion. 5. I am very glad to see that the authors have considered the confounding and sensitivity analyses removing the antidepressants etc. However, I think the authors need to consider the fact that the very fact of why a patient stops taking montelukast could be a confounder. One reason may be the NPAE which makes sense for the analysis at hand and does not create an issue, but is it possible that other reasons (eg montelukast is ineffective for asthma, has other side effects, the patient does not like taking it) may be the cause of some kind of confounding regarding the NPAE outcome? In case-crossover trials the possible confounders eg BMI, comorbidities are reduced/removed

	but those that cause the very reason for different exposures then can have more of an effect. At least this issue should be raised in the section of limitations regarding 'residual confounding'..

REVIEWER NAME	Dr. Yue-E Wu
REVIEWER AFFILIATION	Shandong University No. 44, Wenhua West Road Jinan Shandong 250012 China
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	18-Jun-2024

GENERAL COMMENTS	Kim et al. conducted a study on the relationship of neuropsychiatric adverse events and montelukast use in children and adolescents. It's hard to rule out confounding factors, but the authors came to a conclusion anyway. I have some major concerns about the paper that are detailed below. Major comments 1. Page 4 line 17: The authors mention that there are several related studies with contradictory results. So what is innovative about this study? What are the strengths of this study that make the results more convincing? What are the similarities and differences between this study and other studies? 2. Have the authors considered that the frequency, duration, and dosage of montelukast use are also factors in neuropsychiatric adverse events? 3. How it was determined in the study that the neuropsychiatric adverse event was caused by montelukast? 4. Page 9 line 26: What is the basis for "3-day" "28-day" "56-day"? Please add relevant references? 5. Page 9 line 39: Does "14-day" refer to the number of days after dosing? How to consider the duration of the medication? 6. Page 10 line 56: What is the basis for the age groups? 7. How was desensitization and anonymization achieved? How was data cleaning done and what software was used? 8. Page 12 line 37: How to realize the adjustment for concomitant medications? 9. Page 12 line 47-53: How do the authors explain that the risk of NPAE is highest in children aged 13-19 years? Is it because of differences in drug exposure levels due to different dosages of medication or some other reason?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Bronwyn K. Brew, University of New South Wales Sydney
Comments to the Author

1. In the introduction please briefly summarise the limitations/short comings in the studies that have found no association between montelukast and NPAEs to help justify another study.

Response:
Firstly, we appreciate your time to carefully review the manuscript and give detailed and constructive comments, which has greatly helped to improve this paper. Thank you for your suggestion. We have summarised the limitations of the studies that found no association in the introduction. The amendment made is texted red in the 'manuscript_marked'.

2. In the methods I don't understand how the wash out period can be 5 days when you can see an effect up to 56 days later after prescription. Perhaps the wash out should be longer?

Response:
Initially, during our preliminary analysis, we set the washout period of 14 days, however having to have four control periods of 3-day, 7-day, 14-day, 28-day and 56-day time windows with the 14-day washout period before the hazard period, we lost too many study participants who did not meet aforementioned criteria, and due to the restricted years' worth of data we had, the number of days for the washout period had to be reduced. Considering the maximum mean plasma half-life of montelukast is 5.5 hours in healthy young adults, we decided implementing 5 days washout period seemed plausible.1 In addition, in Korea, we do not have a repeat-prescription system, therefore, based on my personal clinical experience as a community pharmacist, doctors tend to prescribe 3-5 days' worth of montelukast prescription, in which patients have to come back to see doctors in 3-5 days for a repeat prescription. This continues until doctors feel the need to prescribe montelukast for a longer duration. Due to this prescribing system, it was very difficult for us to set longer washout period. Given aforementioned circumstances, we tried our best to implement a suitable washout period. However, I agree with you that the washout period needs to be longer. Time interval between LTRA initiation and neuropsychiatric event can last up to 60 days, although not many NPAE cases are seen between 31 and 60 days.2 (Figure 1) To eradicate any carry-over effect caused by montelukast, setting a longer washout period should be considered. To make this possible, we would need more years' worth of data considering Korean prescribing system. For our future study, we will definitely consider this more thoroughly.

We have attached the figure.
Figure 1. Time interval between drug initiation and neuropsychiatric event. From "Neuropsychiatric side reactions of leukotriene receptor antagonist, antihistamine, and inhaled corticosteroid: a real-world analysis of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS)", by Bian et al, 2021, World Allergy Organ J 14.

References
1. Singulair. Package insert. Merck&Co Inc; 2021.
2. Bian S, Li L, Wang Z, Cui L, Xu Y, et al. Neuropsychiatric side reactions of leukotriene receptor antagonist, antihistamine, and inhaled corticosteroid: a real-world analysis of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). World Allergy Organ J 2021;14:100594.

3. The different hazards windows in Table 2 have the same effect size, I would have expected either a dose response or a maximum effect eg at 4-7 days as others have found with a decrease before and after. Can the authors explain why the effect size would be the same regardless of time?

Response:
We believe that study participants in our study already had a risk factor for experiencing NPAEs. To assure incident cases of NPAEs, we did exclude patients with a history of NPAE diagnosis in the year before the study period. However, we did not eliminate those with a prescription history of antidepressants, antipsychotics and/or benzodiazepines which are prescribed for NPAEs, before the first montelukast prescription. This is because in Korea, diagnostic codes are entered on prescriptions, therefore, using diagnostic codes as one of criteria for selecting study participants in our study would be more accurate than using prescription histories of antidepressants, antipsychotics and benzodiazepines. Due to this reason, although we selected patients who were diagnosed their first NPAE(s) during the study period, there is a chance that patients might have been diagnosed NPAEs in other previous years and continuously have been taking antidepressants, antipsychotics and/or benzodiazepines, and this could have put study patients at higher risk for experiencing NPAEs. Additionally, there is a possibility that doctors might not have entered diagnostic codes for NPAEs when prescribed medications were intended for the treatment of NPAE(s). In Korea, doctors can put multiple diagnostic codes on one prescription. Thus, patients could have visited physicians for different medical conditions apart from NPAEs, but were also prescribed antidepressants, antipsychotics, or benzodiazepines on the same prescriptions. In addition, Kim et al explained the diagnosis in the claims data of HIRA tends to be more accurate in inpatient setting than outpatient cases, and in hospitals rather than clinics.1 Consequently, patients with mild NPAE symptoms who would have presumably visited primary clinics as their first option, may have been at higher risk of having inaccurate diagnostic codes making them potential undetected patients with preexisting NPAE conditions. Subsequently, exposure to montelukast would have contributed an additional risk of NPAEs to these patients.

Reference

1. L Kim, JA Kim, S Kim. A guide for the utilization of Health Insurance Review and Assessment Service National Patient Samples. Epidemiol Health 2014;36:e2014008.

4. I could not find the Pranlukast results in the results section only in the discussion. I suggest they be moved to the results section with only a comment on interpretation and significance in the discussion.

Response:
Once again, thank you for your suggestion. The results of pranlukast were in the supplementary data section, however, we have moved the tables to the results section. Changes made are texted red in 'manuscript_marked'.

5. I am very glad to see that the authors have considered the confounding and sensitivity analyses removing the antidepressants etc. However, I think the authors need to consider the fact that the very fact of why a patient stops taking montelukast could be a confounder. One reason may be the NPAE which makes sense for the analysis at hand and does not create an issue, but is it possible that other reasons (eg montelukast is ineffective for asthma, has other side effects, the patient does not like taking it) may be the cause of some kind of confounding regarding the NPAE outcome? In case-crossover trials the possible confounders eg BMI, comorbidities are reduced/removed but those that cause the very reason for different exposures then can have more of an effect. At least this issue should be raised in the section of limitations regarding 'residual confounding'..

Response:
We agree with your comment on residual confounding. We have added explanations on residual confounding in limitations. Changes made are texted red in 'manuscript_marked'.

Reviewer: 2
Dr. Yue-E Wu, Shandong University
Comments to the Author
Major comments
1. Page 4 line 17: The authors mention that there are several related studies with contradictory results. So what is innovative about this study? What are the strengths of this study that make the results more convincing? What are the similarities and differences between this study and other studies?

Response:
Firstly, we appreciate your time to carefully review the manuscript and give detailed and constructive comments, which has greatly helped to improve this paper.
To the best of our knowledge, this is the first case-crossover study observing the risk of NPAEs associated with montelukast use in children and adolescents using the most recent population-level claims database. The case-crossover study design itself effectively controls both known and unknown confounders, such as gender, socioeconomic factors, and genetic factors. NPAEs are highly associated with genetic factors, therefore, the use of case-crossover study design would resolve the issue.1 In addition, the study design allows study subjects to act as their own controls minimising intersubject variability. Furthermore, our study used the most recent database available at a population level from 2018 to 2021, which would have reflected the reality more effectively. To our knowledge, apart from our study, the most recent data used to examine the association between montelukast and NPAEs were between 2016 and 2018 from a SCCS study.2 It is pertinent to include the most recent data possible as the FDA's announcement regarding strengthening of boxed warning of NPDs on montelukast occurred in 2020, and it is possible that the announcement could have affected how NPAEs diagnosed in paediatric patients exposed to montelukast. To avoid potential bias, our customised HIRA data were from 2018 to 2021 which contained claims data both before and after the FDA's announcement. We conducted additional analyses investigating the relationship between the use of pranlukast and the risk of developing NPAEs. Other previous studies observed the association either between montelukast and the risk of NPAEs or between LTRAs and the risk of NPAEs. To our knowledge, no study had examined the association between pranlukast and the risk of NPAEs. Studies that were conducted to see if LTRAs caused an increase in the risk of NPAEs, cannot decisively conclude whether both montelukast and pranlukast or montelukast and pranlukast respectively contributed to the increased risk of NPAEs unless additional analyses on pranlukast were conducted. In fact, no warning regarding the risk of NPAEs on pranlukast has been made, and it is still not clear if pranlukast was also associated with NPAEs. Considering montelukast and pranlukast belong to the same class of medication, LTRA where the mechanism of action of each medication is known to be similar, we believe it is necessary to conduct analyses on pranlukast as well. Based on our findings, comparable to montelukast, pranlukst showed an increased risk of NPAEs in paediatric patients with allergic rhinitis and/or asthma. However, more studies need to be performed to conclusively confirm the association between pranlukst and the risk of NPAEs.
In comparison to nested case-control studies, our results showed several similar findings. A study by Glockler-Lauf et al3, found children with asthma who had an experience of a new onset of NPAE had almost twice the odds of having been administered montelukast in comparison to controls (OR 1.91; 95% CI 1.15-3.18).3 Most diagnosed cases were anxiety (48.6%).3 Comparably, the most common NPAE in our study was also anxiety (29.69%). The risk from Glockler-Lauf et al3 was higher than that of ours (aOR 1.38; 95% CI 1.36-1.41 in 28-day time window). This could be due to asthma condition

itself. One of the studies suggested an interesting point that chronic montelukast treatment was not associated with depression-like behaviours, but confirmed the association between depression and asthma in mice.4 Thus, it is possible that asthma condition itself could be one of the possible reasons for the increased risk for psychiatric conditions like depression. Moreover, a cohort study by Paljarvi et al5 showed the risk of any NPAE incident outcomes was higher in patients with asthma compared to those with allergic rhinitis.5 Considering Glockler-Lauf et al3 only included asthmatic patients, whereas our study included both asthmatic and patients with allergic rhinitis, it is reasonable to explain our risk was considerably lower than that of Glocker-Lauf's.
Our findings on the increased risk of NPAEs regarding montelukast use within 3, 7, and 14 days of the hazard period were consistent with a SCCs study. A SCCS study showed increased risks in the 4-7 and 8-14 days after initiation of LTRAs, and a study by Bian et al6, found most reported cases of NPAEs occurred with the first 10 days since drug intiation.2,6 In addition, the SCCS study identified a notable risk predominantly in adolescents (IRR 1.28; 95% CI 1.05-1.55), while the risk decreased in children aged between 3 and 11 years.2 A similar finding was seen in our study in which the risk of NPAEs was the highest in children and adolescents aged 13-19 years, and the lower risk was shown in patients aged 0-9 years. However, in our study, the risk of NPAEs remained elevated in 28 days, and 56 days of the hazard period, whereas the risk was not found in 15-30, 31-90, and >90 days since LTRA initiation in an SCCS study.2

References
1. Lewer D, Petersen I, Maclure M. The case-crossover design for studying sudden events. BMJ Med 2022;1:e000214.
2. Park J, Cho Y, Yun J, Lee H, Yu J, et al. Leukotriene receptor antagonists and risk of neuropsychiatric events in children, adolescents and young adults: a self-controlled case series. Eur Respir J 2021;60:2102467.
3. Glockler-Lauf S, Finkelstein Y, Zhu J, Feldman L, To T. Montelukast and neuropsychiatric events in children with asthma: a nested case-control study. J Pediatr 2019;209:176-182.
4. Tel B, Telli G, Onder S, Nemutlu E, Bozkurt T. Investigation of the relationship between chronic montelukast treatment, asthma and depression-like behavior in mice. Exp Ther Med 2021;21:https://doi.org/10.3892/etm.2020.9459.
5. Paljarvi T, Forton J, Luciano S, Herttua K, Fazel S. Analysis of neuropsychiatric diagnoses after montelukast initiation. JAMA Netw Open 2022;5:e221343.
6. Bian S, Li L, Wang Z, Cui L, Xu Y, et al. Neuropsychiatric side reactions of leukotriene receptor antagonist, antihistamine, and inhaled corticosteroid: a real-world analysis of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). World Allergy Organ J 2021;14:100594.

2. Have the authors considered that the frequency, duration, and dosage of montelukast use are also factors in neuropsychiatric adverse events?

Response:
We did consider the duration of montelukast treatment as one of the factors associated with NPAEs. However, based on previous studies, the onset of montelukast-related NPAEs is usually between 7 and 14 days, and given the fact that our study used a case-crossover design, which is applicable when the exposure to montelukast is intermittent and the onset of outcome is abrupt like NPAEs, we thought the duration of montelukast treatment would not be an issue in our case.1,2,3 In terms of dosage, montelukast has an age-specific dosage. 4mg of montelukast can be given to infants, toddlers and children aged from 6 months to 5 years, 5mg from 6 years old, and 10mg from 15 years old to adults, and should always be administered once daily.5 For example, even if the child weighed like an adult, still montelukast should be given based on the child's age, not weight.5 Therefore, we decided the dosage of montelukast would not be a key contributing factor to NPAEs. However, we considered the frequency of montelukast administration could be one of the factors. As mentioned in our study, montelukast is often taken intermittently for symptomatic relief of asthma exacerbations and treatment of allergic rhinitis. People with severe symptoms may take it for weeks, and those with milder symptoms might take montelukast for only several days. Due to this reason, we set four control periods rather than three considering the prescribing pattern of montelukast to take frequency of montelukast into consideration. However, because we used claims data where we cannot be certain about whether patients were compliant to montelukast, having more control periods may not resolve the issue. To minimise the effect of this problem, setting more sophisticated study criteria like dividing study participants into different categories based on the number of montelukast scripts prescribed during certain time frame can be one of the options. This solution would be more appropriate to use in cohort studies, therefore, we are planning to take aforementioned considerations into account in our future study.

References
1. Park J, Cho Y, Yun J, Lee H, Yu J, et al. Leukotriene receptor antagonists and risk of neuropsychiatric events in children, adolescents and young adults: a self-controlled case series. Eur Respir J 2021;60:2102467.
2. Glockler-Lauf S, Finkelstein Y, Zhu J, Feldman L, To T. Montelukast and neuropsychiatric events in children with asthma: a nested case-control study. J Pediatr 2019;209:176-182.
3. Bian S, Li L, Wang Z, Cui L, Xu Y, et al. Neuropsychiatric side reactions of leukotriene receptor

antagonist, antihistamine, and inhaled corticosteroid: a real-world analysis of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). World Allergy Organ J 2021;14:100594.
4. Singulair. Package insert. Merck&Co Inc; 2021.

3. How it was determined in the study that the neuropsychiatric adverse event was caused by montelukast?

Response:
Considering the nature of our case-crossover study design, montelukast exposure immediately before the hazard period (the diagnosis of NPAE) was considered as the NPAE caused by montelukast. To assure incident cases of NPAEs that can be possibly caused by montelukast, we have excluded patients with prior diagnosis of NPAEs in 2017, which was one year before our study period. Moreover, patients who newly started concomitant medications after montelukast exposure, but before the first diagnosis of NPAEs were excluded from the study to assure montelukast-associated NPAEs.

4. Page 9 line 26: What is the basis for "3-day" "28-day" "56-day"? Please add relevant references?

Response:
We have set 3-day, 14-day, 28-day, and 56-day time windows in our study in reference to other previous Korean studies such as Park et al that observed the association between the risk of NPAEs and montelukast use using a self-controlled case series study, and Kang et al which used a case-crossover study design to observe the risk of NPAEs and oseltamivir use.1,2 Our study used a case-crossover study design indicating that exposure to montelukast is transient when used for symptomatic relief of allergic rhinitis and the treatment of asthma exacerbations, and the onset of NPAE outcomes is abrupt. Therefore, the implementation of 3-day and 14-day time windows deemed feasible in our study. In addition, based on my personal clinical experience as a community pharmacist in Korea, when paediatricians prescribe montelukast, the minimum number of days' supply for montelukast prescription is usually 3 days. Physicians usually prescribe 5 to 14 days' worth of montelukast as montelukast is often used for the symptomatic relief of allergic rhinitis, which is considered as a short-term treatment. In terms of setting 28-day and 56-day time windows, the time interval between LTRA initiation and neuropsychiatric event lasted up to 60 days according to a study conducted by Bian et al.3 (Figure 1) Additionally, we wanted to observe the long-term effects of montelukast, additional 28-day and 56-day time windows were included in the study.

We have attached the figure.
Figure 1. Time interval between drug initiation and neuropsychiatric event. From "Neuropsychiatric side reactions of leukotriene receptor antagonist, antihistamine, and inhaled corticosteroid: a real-world analysis of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS)", by Bian et al, 2021, World Allergy Organ J 14.

References
1. Park J, Cho Y, Yun J, Lee H, Yu J, et al. Leukotriene receptor antagonists and risk of neuropsychiatric events in children, adolescents and young adults: a self-controlled case series. Eur Respir J 2021;60:2102467.
2. Kang H, Lee E, Kim W, Shin J. Risk of neuropsychiatric adverse events associated with the use of oseltamivir: a nationwide population-based case-crossover study. J Antimicrob Chemother 2019;74:453-461.
3. Bian S, Li L, Wang Z, Cui L, Xu Y, et al. Neuropsychiatric side reactions of leukotriene receptor antagonist, antihistamine, and inhaled corticosteroid: a real-world analysis of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). World Allergy Organ J 2021;14:100594.

5. Page 9 line 39: Does "14-day" refer to the number of days after dosing? How to consider the duration of the medication?

Response:
A 14-day time window refers to the exposure to montelukast prescription within 14 days of the hazard period (the diagnosis of NPAE). Unfortunately, due to the nature of claims dataset, we cannot be certain about the actual duration of montelukast that was genuinely taken by the patient in which we consider it as residual confounding.

6. Page 10 line 56: What is the basis for the age groups?

Response:
The reason for the choice aggregation was that the HIRA dataset we used had aggregated age groups of 0-2, 3-5, 6-9, 10-12 and 13-19 years in the paediatric population.

7. How was desensitization and anonymization achieved? How was data cleaning done and what software was used?

Response:
The HIRA data must provide data without individual identifiers by utilising an unidentifiable code representing each individual as per the "Act on the Protection of Personal Information Maintained by Public Agencies".1 Once the approval for the researcher's study is given, HIRA extracts the requested data from the Data Warehouse. Information on ID in the data are encrypted to protect private information.2 We are not sure about what software was used for data cleaning as information is not provided publicly.

References
1. Kim HK, Song SO, Noh J, et al. Data configuration and publication trends for the Korean National Health Insurance and Health Insurance Review & Assessment Database. Diabetes Metab J 2020;44:671-678.
2. Kim JA, Yoon S, Kim LY, et al. Towards actualising the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. J Korean Med Sci 2017;32:718-728.

8. Page 12 line 37: How to realize the adjustment for concomitant medications?

Response:
We have defined concomitant medications as antidepressants, antiepileptics, antihistamines, antipsychotics, benzodiazepines, corticosteroids, histamine H2-receptor antagonists, neuraminidase inhibitors, NSAIDs, opioids, psychostimulants in reference to previous studies that observed NPAEs, and these were checked by Dr Mideum Kim, one of our authors for suitability.1,2,3 (Supplementary table S3) We have adjusted each class of concomitant medications individually using conditional logistic regression. For example, if patients took antidepressants, we classified them as antidepressant users and applied to the analysis. After the adjustment for concomitant medications, the overall risk elevated slightly compared.

References
1. Park J, Cho Y, Yun J, Lee H, Yu J, et al. Leukotriene receptor antagonists and risk of neuropsychiatric events in children, adolescents and young adults: a self-controlled case series. Eur Respir J 2021;60:2102467.
2. Kang H, Lee E, Kim W, Shin J. Risk of neuropsychiatric adverse events associated with the use of oseltamivir: a nationwide population-based case-crossover study. J Antimicrob Chemother 2019;74:453-461.
3. Paljarvi T, Forton J, Luciano S, Herttua K, Fazel S. Analysis of neuropsychiatric diagnoses after montelukast initiation. JAMA Netw Open 2022;5:e221343.

9. Page 12 line 47-53: How do the authors explain that the risk of NPAE is highest in children aged 13-19 years? Is it because of differences in drug exposure levels due to different dosages of medication or some other reason?

Response:
We believe the highest risk of NPAEs was found in children and adolescents aged 13-19 years, because of an increased diagnosis of mental health diagnosis in this particular age group. A study by Glassgow et al compared prevalence of mental health diagnoses in three different age groups, 5-8 years, 9-13 years, and 14-18 years.1 The highest risk of mood disorders and anxiety disorders respectively was seen in 14-18 years.1 Another study conducted by Ghandour RM et al showed a comparable result where diagnoses of ADHD, anxiety, and depression were more common with increased age.2 A higher risk of NPAEs after LTRA initiation in adolescents and young adults (13-19 years) was also noted in a SCCS study.3 Similarly, in our study, 40% of study participants were aged between 13 and 19 years, anxiety disorders and mood disorders were the most diagnosed NPAEs (29.7% for anxiety disorders and 28.6% for personality disorders), and the highest risk was found in the adolescents compared those in other age groups. Regardless of the effect of montelukast, the age-specific onset of any mental disorders is generally the highest in adolescence, and in fact, young adults aged 18-25 years had the highest prevalence of any mental illness (33.7%) compared to adults.4 In addition, seeing a higher risk of psychiatric conditions in adolescents could be because it is easier for psychiatrists to make diagnoses in adolescents compared to infants and toddlers resulting in more diagnoses of neuropsychiatric conditions in 13-19 years patients, and our study used data that included the COVID-19 pandemic period which could have attributed to more diagnoses of depression and anxiety disorders in adolescents when their social skills were still developing, but the skills were worsened by the pandemic.5,6

References
1. Glassgow A, Wilder J, Caskey R, et al. Mental health diagnoses among children and adolescents with chronic medical conditions in a large urban cohort. J Behav Health 2020;9:1-8.
2. Ghandour RM, Sherman LJ, Vladutiu CJ, et al. Prevalence and treatment of depression, anxiety, and conduct problems in US children. J Pediatr 2019;206:256-267.
3. Park J, Cho Y, Yun J, Lee H, Yu J, et al. Leukotriene receptor antagonists and risk of neuropsychiatric events in children, adolescents and young adults: a self-controlled case series. Eur Respir J 2021;60:2102467.

4. National Institute of Mental Health. NIMH» Mental Illness [Internet]. www.nimh.nih.gov. 2022. Available from: https://www.nimh.nih.gov/health/statistics/mental-illness#part_2539
5. Racine N, McArthur B, Cooke J, Eirich R, Zhu J, et al. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: A meta-analysis. JAMA Pediatr 2021;175:1142-1150.
6. Lee J, Hong S, Kim K. Mental health of adolescents and subjective economic deterioration caused by COVID-19 in Korea. J Korean Med Sci 2022;37:e268.