Asian Journal of Psychiatry 92 (2024) 103894

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Letter to the Editor

Effect of metformin on the risk of depression: A systematic review and meta-regression of observational studies

ARTICLE INFO

Keywords
Metformin
Depression
Repurposing
Asian population
Meta-regression

1. Introduction

Depression, a common mood disorder, affects more than 280 million people around the globe (World Health Organization, 2023). Despite the increasing use of antidepressants, patients with depression do not always experience symptom alleviation due to varying responsiveness to antidepressant monotherapy (Rush et al., 2006). Metformin is a first-line treatment for type 2 diabetes mellitus. Preclinical and clinical studies found that metformin reduced depressive-like behaviors by modulating the balance of proinflammatory markers, brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-I), the cytokines and neurotrophic markers consistent with the pathogenesis of depression, therefore suggesting the possibility of repurposing metformin as antidepressant monotherapy or adjunctive to current treatments (Fang et al., 2020; Hammad et al., 2021; Karnevi et al., 2013). Recently, two meta-analyses of randomized controlled trials (RCTs) investigated the effect of metformin or anti-glycaemic drugs and cognition and depression in general patients, but they showed inconsistent results and were restricted to a limited number of included studies with varied quality (Moulton et al., 2018; Nibber et al., 2022). The results from relevant observational studies to date have been less discussed. Therefore, we aimed to evaluate the potential of metformin in alleviating depression and explore subgroups that would most likely benefit from treatment by systemically aggregating evidence from observational studies.

2. Methods

The study protocol is pre-registered with PROSPERO (CRD42023398184). We systematically searched four databases, including PubMed, Cochrane, Web of Science, and Embase, using designated search terms updated to 19 October 2022 to identify literature reporting the risk of depression following metformin use (Supplementary Table 1). We included quantitative observational studies in which odds ratios (OR), relative risk (RR), or hazard ratios (HR) for 95% confidence intervals (CI) were provided or could be calculated. We excluded reviews, abstracts, unpublished results, non-English articles, and studies in which metformin was used in combination with other interventions. The Newcastle-Ottawa Scale and the Agency for Healthcare Research and Quality Scale were used to assess the quality of included studies (Supplementary Table 2).

All statistics were performed using STATA/SE 17 (StataCorp LLC, Texas, USA) and R 4.1.3. Based on the study design (cohort, case-control, and cross-sectional studies), separate meta-analyses by random effects models were conducted to calculate the combined effect size for the association between metformin use and the risk of depression. Heterogeneity was assessed by the I-squared index (I^2). Subgroup analysis was performed stratified by indications (Diabetes mellitus, DM; Polycystic Ovary Syndrome, PCOS; General population) and regions (Asia, Europe, Oceania) to assess the effects of metformin on different populations after combining all studies with pooled effect size (ES). Univariate meta-regression was conducted to explore the sources of heterogeneity, and covariates included year of publication, indications, female proportion (%), regions (Asia, Europe, or Oceania), and identification of depression (self-reported questionnaires or medical records/clinical interviews). Sensitivity analysis determined whether the quality of publications affected the overall effect size. Funnel plot, and Egger's weighted regression statistics were performed to assess publication bias (Supplementary Fig. 1). Two researchers (YZ and VC) performed the screening, data extraction, evaluation, and analyses independently.

3. Results

11 studies were included in the qualitative synthesis and their characteristics and results are shown in Fig. 1. Flowchart and characteristics of eligible studies are shown in Supplementary Fig. 2 and Supplementary Table 3. The included studies were published between 2006 and 2022 and were conducted in 10 countries or territories. A total of nine studies were included in the final analysis after excluding two studies that did not report required risk estimates.

Pooled estimates from four cohort studies showed a reduced but not significant risk of depression among metformin users compared with non-metformin users (RR: 0.69, 95% confidence interval (CI): 0.46–1.02, $p = 0.06$, $I^2 = 53.5\%$) (Fig. 2). In three case-control studies, patients with metformin had a significantly lower risk of depression than

https://doi.org/10.1016/j.ajp.2023.103894
Received 4 November 2023; Received in revised form 18 December 2023; Accepted 20 December 2023
Available online 23 December 2023

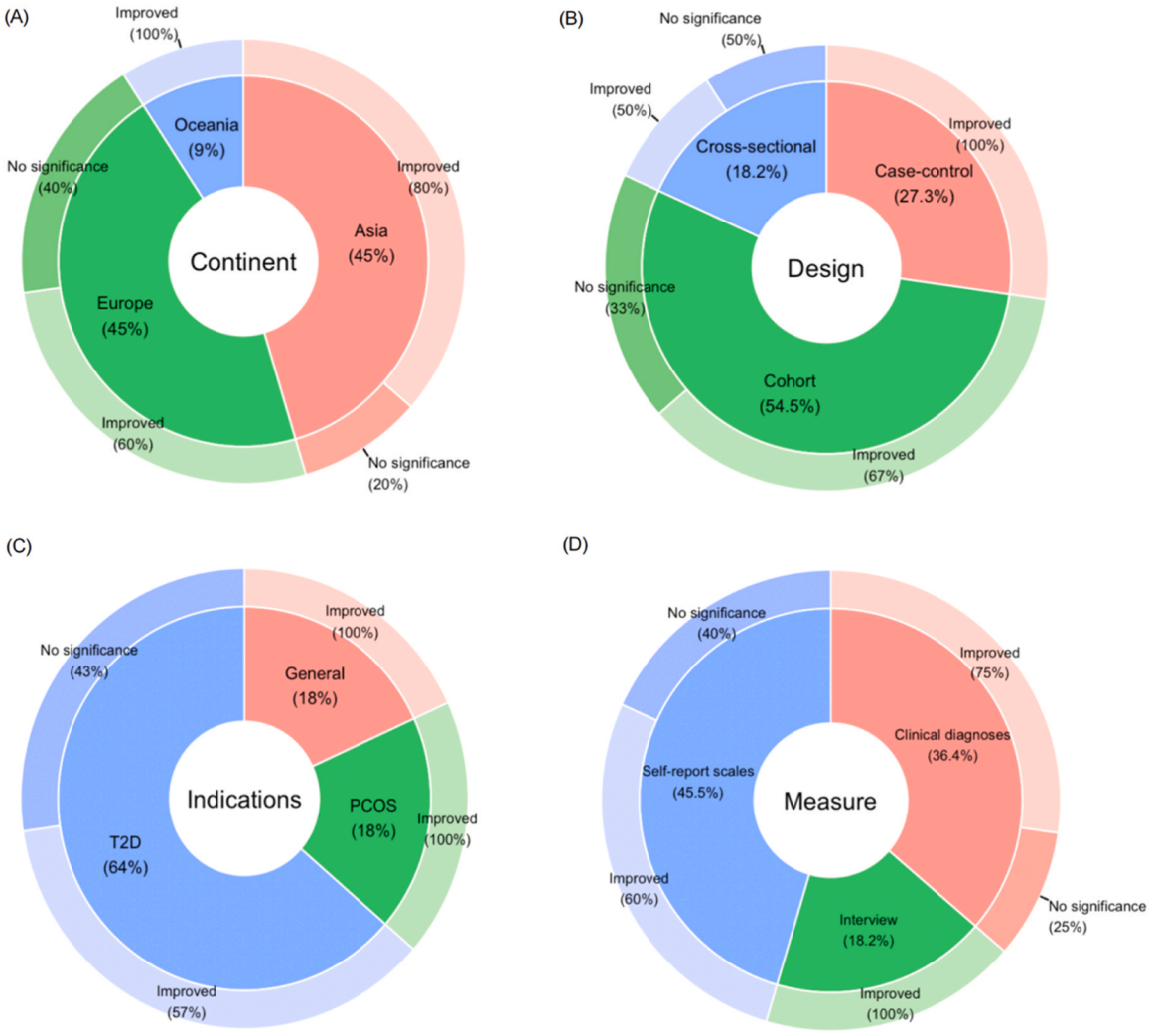

Fig. 1. Characteristics of the studies included in the systematic review and their results. Note: (A) The inner circle represents the inclusion of studies divided into three subcategories based on continent. The outer circle indicates the results of the effect of metformin on depression in the included studies. (B) Effects of metformin on depression base on study designs; (C) Indications; (D) Measures of depression. Abbreviations: Improved: indicates improvement of depression by metformin; No significance: no significant effect of depression by metformin; T2D = Type 2 diabetes; PCOS = Polycystic Ovary Syndrome; General: General population.

those without (OR: 0.92, 95%CI: 0.89–0.96, $p < 0.001$, I^2=34.9%). In two cross-sectional studies, the association between metformin use and depression risk was not significant.

In the subgroup analysis by region, metformin use significantly reduced the risk of depression in five studies involving 520,557 participants in Asia (ES=0.67, 95% CI=0.50–0.91, $p = 0.011$), and within-group heterogeneity was reduced (I^2=48.9%); the relationship between metformin and depression was not significant in three studies involving 542,304 participants in Europe (ES: 0.95, 95%CI: 0.89–1.02, $P = 0.130$, I^2=50.3%, Supplemental Fig. 3). Additionally, subgroup analysis by indication showed no significant association. Univariate meta-regression showed that the association between metformin and risk of depression was significantly linked to continent (b=0.43, $P = 0.02$, I-squared_res=49.28%, Adj R-squared=48.30%). None of the other factors explained the observed heterogeneity between studies (Supplemental Fig. 4).

4. Discussion

This study found that metformin was significantly associated with decreased risk of depression in case-control studies but not in other study designs. One of two previous meta-analyses of RCTs showed that metformin did not significantly reduce depressive symptoms compared to placebo (Moulton et al., 2018). The meta-analysis included three small placebo-controlled RCTs with high heterogeneity (I^2=92.3%), including one unpublished study. The second meta-analysis indicated that metformin also showed some antidepressant properties in patients with depression and T2D compared with placebo; the effect was insignificant compared with pioglitazone (Nibber et al., 2022).

Limited evidence from the RCTs and high heterogeneity reflect the need for real-world evidence aggregation. This study's synthesis of observational studies involving over 1 million participants, a mean follow-up time of 9.4 years in cohort and nested case-control studies, would be valuable supporting evidence. An interesting finding of this meta-analysis was that metformin was associated with a significantly reduced risk of depression in Asian populations. Among the risk factors examined in the meta-regression, only the continent explained part of the observed heterogeneity ($P = 0.02$). This is possibly attributed to differences in life or social determinants and genetic differences between populations. Factors such as differences in lifestyle, dietary habits, economic disparities, and education levels in different populations may play a role (Lankarani and Assari, 2015). Furthermore, the difference in inflammatory status may also underlie differences in the risk assessment of metformin for depression between populations (Beydoun et al., 2020).

Due to the limited variables of the included studies in this systematic

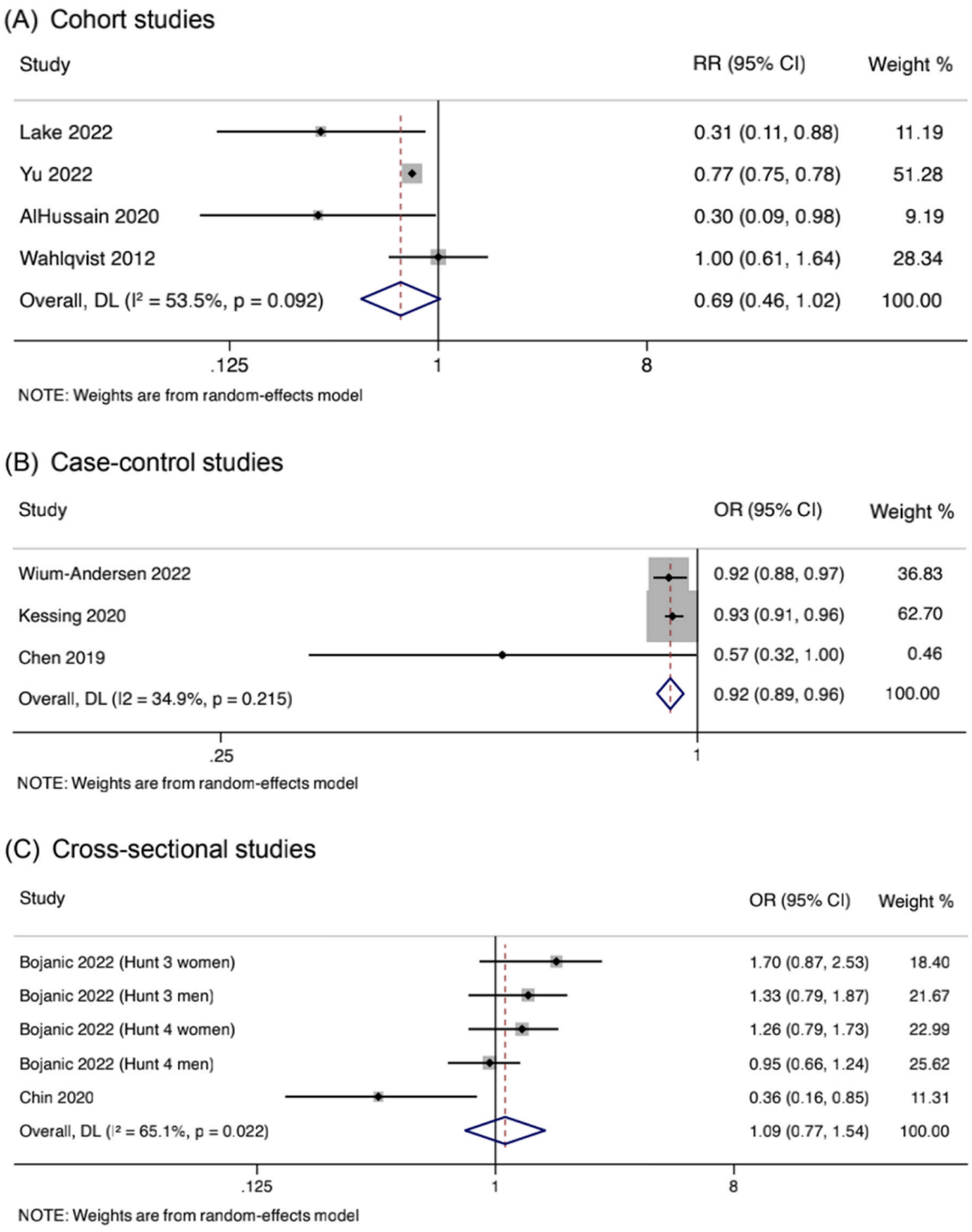

Fig. 2. Forest plots of effects of metformin on depression in observational studies with different study designs. Note: (A) Cohort studies; (B) Case-control studies; (D) Cross-sectional studies.

review, further comparisons for differences between Asian populations and other populations, such as glucose control, dietary structure and medication adherence, were not feasible. The biological mechanisms of this ethnically specific effect of metformin on depression merit further investigation. Additionally, most included studies (6 out of 9) were conducted among patients with diabetes with inconsistent findings. Diabetes is associated with a greater risk of depression and anxiety (Jaisoorya et al., 2022). Current literature suggested an association between glycaemic control with risk and severity of depression in patients with diabetes (Papelbaum et al., 2011), and certain antidepressants have a positive effect on glycaemic control (Zhang et al., 2022). Therefore, the additional consideration of glycaemic control in subsequent studies would be valuable in investigating biological pathways that might link metformin use with a potential reduction in the risk of depression. Also, it was shown that antidepressant treatment during pregnancy may increase the risk of pregnancy and neonatal complications (Su et al., 2023), so further study on the effect of metformin at different periods would be beneficial.

Based on the underlying anti-depression properties of metformin observed in this study, the potential of repurposing metformin for depression control is possible but it warrants well-designed RCTs in selected populations. In particular, our findings indicate that metformin may be a promising anti-depression therapy for Asians, inviting more research into mechanisms behind racial differences to suggest potentially more targeted treatments. Study limitations include the limited number of included studies may affect the stability of the results and statistical hence the heterogenicity observed. In addition, relationship between metformin and depression may be mediated by glycemic control; hence a more elaborate study design would be worthwhile (Kyriacou and Lewis, 2016).

In conclusion, reduced risk of depression associated with metformin was observed in case-control studies, but not significant in cohort studies. Regional differences were observed. Metformin may have the potential to be repurposed to improve depression management, particularly in the Asian population. The biological mechanism of ethics-specific effect warrants further investigation.

Financial disclosure

This research was funded by Research Grant Council, Research Impact Fund (Ref: R7007–22F). The funder has no role in the study design, data collection, data analysis, data interpretation and writing of the report.

CRediT authorship contribution statement

Wong Ian Chi Kei: Conceptualization, Writing – review & editing. **Li Xue:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. **Chan Esther Wai Yin:** Writing – review & editing. **Lee Chi Ho:** Writing – review & editing. **Chan Sandra Sau Man:** Writing – review & editing. **Zhang Yin:** Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Chan Vivien Kin-Yi:** Data curation, Investigation, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

XL received research grants from Research Fund Secretariat of the Health Bureau, Health and Medical Research Fund (HMRF, HKSAR), Research Grants Council Early Career Scheme (RGC/ECS, HKSAR), Research Grants Council Research Impact Fund (RGC/RIF, HKSAR), educational and investigator initiate research fund from Janssen and Pfizer; internal funding from the University of Hong Kong; consultancy fee from Merck Sharp & Dohme, unrelated to this work. EWYC reports honorarium from Hospital Authority; and grants from Research Grants Council (RGC, Hong Kong), Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda, and Narcotics Division of the Security Bureau of the Hong Kong Special Administrative Region, outside the submitted work. ICKW reports grants from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK and Novartis, the Hong Kong RGC, and the Hong Kong Health and Medical Research Fund in Hong Kong, National Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, consulting fees from IQVIA and World Health Organization, payment for expert testimony for Appeal Court of Hong Kong and is a non-executive director of Jacobson Medical in Hong Kong and Therakind in England, outside of the submitted work; no other relationships or activities that could appear to have influenced the submitted work. All other authors have no reports on conflict of interest.

Acknowledgement

We thank Ms Awasthi Swambhavi for her contribution to the data extraction. We also thank Ms Lisa Lam for English proof-reading.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2023.103894.

References

Beydoun, M.A., Obhi, H.K., Weiss, J., Canas, J.A., Beydoun, H.A., Evans, M.K., Zonderman, A.B., 2020. Systemic inflammation is associated with depressive symptoms differentially by sex and race: a longitudinal study of urban adults. Mol. Psychiatry 25 (6), 1286–1300. https://doi.org/10.1038/s41380-019-0408-2.

Fang, W., Zhang, J., Hong, L., Huang, W., Dai, X., Ye, Q., Chen, X., 2020. Metformin ameliorates stress-induced depression-like behaviors via enhancing the expression of BDNF by activating AMPK/CREB-mediated histone acetylation. J. Affect. Disord. 260, 302–313. https://doi.org/10.1016/j.jad.2019.09.013.

Hammad, A.M., Ibrahim, Y.A., Khdair, S.I., Hall, F.S., Alfaraj, M., Jarrar, Y., Abed, A.F., 2021. Metformin reduces oxandrolone-induced depression-like behavior in rats via modulating the expression of IL-1β, IL-6, IL-10 and TNF-α. Behav. Brain Res. 414, 113475 https://doi.org/10.1016/j.bbr.2021.113475.

Jaisoorya, T., Bhaskarapillai, B., Manoj, L., Kumar, G.S., Gokul, G., Thennarasu, K., 2022. Risk estimates of anxiety and depressive disorders among primary care patients with chronic medical illness–a Indian study. Asian J. Psychiatry 74, 103190.

Karnevi, E., Said, K., Andersson, R., Rosendahl, A.H., 2013. Metformin-mediated growth inhibition involves suppression of the IGF-I receptor signalling pathway in human pancreatic cancer cells. BMC Cancer 13 (1), 11. https://doi.org/10.1186/1471-2407-13-235.

Kyriacou, D.N., Lewis, R.J., 2016. Confounding by indication in clinical research. JAMA 316 (17), 1818–1819. https://doi.org/10.1001/jama.2016.16435.

Lankarani, M.M., Assari, S., 2015. Association between number of comorbid medical conditions and depression among individuals with diabetes; race and ethnic variations. J. Diabetes Metab. Disord. 14 (1), 1–8. https://doi.org/10.1186/s40200-015-0171-0.

Moulton, C.D., Hopkins, C.W.P., Ismail, K., Stahl, D., 2018. Repositioning of diabetes treatments for depressive symptoms: a systematic review and meta-analysis of clinical trials. Psychoneuroendocrinology 94, 91–103. https://doi.org/10.1016/j.psyneuen.2018.05.010.

Nibber, A., Singh, H., Burnet, P., Lennox, B., Minichino, A., 2022. Investigating the pro-cognitive and anti-depressant efficacy of metformin: a systematic review and meta-analysis of randomised controlled trials. J. Affect. Disord. https://doi.org/10.1016/j.jad.2022.04.156.

Papelbaum, M., Moreira, R.O., Coutinho, W., Kupfer, R., Zagury, L., Freitas, S., Appolinário, J.C., 2011. Depression, glycemic control and type 2 diabetes. Diabetol. Metab. Syndr. 3 (1), 1–4. https://doi.org/10.1186/1758-5996-3-26.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. Am. J. Psychiatry 163 (11), 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905.

Su, J.-A., Chang, C.-C., Yang, Y.-H., Lee, C., Chen, K.-J., Lin, C.-Y., 2023. Neonatal and pregnancy complications following maternal depression or antidepressant exposure: a population-based, retrospective birth cohort study. Asian J. Psychiatry 84, 103545. https://doi.org/10.1016/j.ajp.2023.103545.

World Health Organization. (2023 March 31). Depressive disorder (depression). from https://www.who.int/news-room/fact-sheets/detail/depression. (Accessed 31 March 2023).

Zhang, Z., Du, Y., Chen, L., Liu, Y., Du, B., 2022. Effects of the selective serotonin re-uptake inhibitor fluoxetine on glucose metabolism: a systematic review. Asian J. Psychiatry 73, 103092.

Yin Zhang[1]

Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region of China

Vivien Kin-Yi Chan[2]

Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region of China

[1] Co-first author with equal contribution.

[2] Co-first author with equal contribution.

Sandra Sau Man Chan
Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region of China

Esther Wai Yin Chan
Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region of China
Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Sha Tin, Hong Kong Special Administrative Region of China

Chi Ho Lee
Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region of China

Ian CK Wong
Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region of China
Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Sha Tin, Hong Kong Special Administrative Region of China
Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom
Aston School of Pharmacy, Aston University, Birmingham, United Kingdom

Xue Li*
Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region of China
Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region of China
Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Sha Tin, Hong Kong Special Administrative Region of China

* Correspondence to: Department of Medicine & Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, PB306, 3/F, Professional Block, Queen Mary Hospital, 102 Pok Fu Lam Road, Hong Kong Special Administrative Region of China.
E-mail address: sxueli@hku.hk (X. Li).