J Nephropharmacol. 2024; 13(1): e11651.

https://jnephropharmacology.com DOI: 10.34172/npj.2023.11651

Journal of Nephropharmacology

The association between metformin administration and non-Hodgkin lymphoma; a systematic review and meta-analysis of cohort and case-control studies

Elnaz Ataei[1], Razieh Bagheri Shahzadeh Aliakbari[2], Navid Asgari[3], Nasim Zaman Samghabadi[4], Sina Salati[5], Sara Abbasian[6], Mohammad Akbari[7], Farshad Gharebakhshi[8,9], Anna Ghorbani Doshantapeh[10*]

[1]Clinical Research Development Center, Shahid Modarres Educational Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Biomedical Engineering and Rehabilitation Sciences, Louisiana Tech University, Ruston, Louisiana, USA
[3]Department of Internal Medicine, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Department of Infectious Diseases, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[5]Department of Nursing, Kashmar School of Medical Sciences, Mashhad University of Medical Sciences, Mashhad, Iran
[6]Department of Nursing, Faculty of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran
[7]Department of Nursing, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[8]Department of Radiology, Imam Hossein Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[9]Guissu Research Corporation, Bandar Abbas, Iran
[10]Department of Hematology-Medical Oncology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article Type:
Meta-analysis

Article History:
Received: 10 July 2023
Accepted: 1 November 2023
ePublished: 27 November 2023

Keywords:
Metformin
Metformin hydrochloride
Glucophage
Non-Hodgkin lymphoma
Reticulum cell sarcoma
Pleomorphic lymphoma
Undifferentiated lymphoma

ABSTRACT

Introduction: Metformin, a blood sugar-lowering agent, has the potential to be an anti-cancer agent. However, its role in lymphoma remains uncertain.

Objectives: This study sought to examine the correlation between the utilization of metformin and non-Hodgkin lymphoma through the application of a systematic review and meta-analysis methodology.

Materials and Methods: This investigation was carried out in the form of a methodical examination and meta-analysis in accordance with the PRISMA guidelines. Databases such as Scopus, PubMed, Web of Science, Cochrane, and the Google Scholar search engine were thoroughly explored without any temporal limitations until September 20, 2023. The data was analyzed utilizing the STATA 14 software, and the level of significance for the tests was established at $P<0.05$.

Results: The results, obtained by combining six observational studies (five cohort studies and one case-control study) with a total sample size of 2 330 787 individuals, showed that the odds ratio (OR) for the association between metformin use and non-Hodgkin lymphoma in all studies was 0.91 (95% CI: 0.78, 1.07). In cohort studies, the OR was 0.91 (95% CI: 0.74, 1.11), and in the case-control study, it was 0.93 (95% CI: 0.79, 1.10). None of these relationships were statistically significant. The odds ratio between metformin uses and chronic lymphocytic leukemia/small lymphocytic leukemia was 0.93 (95% CI: 0.71, 1.21), and the odds ratio between metformin use and diffuse large B-cell lymphoma was 1.06 (95% CI: 0.61, 1.83), both of which were not statistically significant.

Conclusion: This investigation's findings indicated no statistically noteworthy correlation exists between the utilization of metformin and the probability of contracting non-Hodgkin lymphoma, chronic lymphocytic leukemia/small lymphocytic leukemia, and diffuse large B-cell lymphoma.

Registration: This study was conducted following the PRISMA checklist. Its protocol was registered on the PROSPERO (CRD42023469100) and Research Registry (UIN: reviewregistry1721) websites.

Implication for health policy/practice/research/medical education:
The results, obtained by combining six observational studies (five cohort studies and one case-control study) with a total sample size of 2 330 787 individuals, showed that metformin has no significant effect on the occurrence of non-Hodgkin lymphoma, chronic lymphocytic leukemia/small lymphocytic leukemia, and diffuse large B-cell lymphoma. However, considering the aforementioned limitations and the limited number of studies, it appears that more research studies are needed.

Please cite this paper as: Ataei E, Bagheri Shahzadeh Aliakbari R, Asgari N, Zaman Samghabadi N, Salati S, Abbasian S, Akbari M, Gharebakhshi F, Ghorbani Doshantapeh A. The association between metformin administration and non-Hodgkin lymphoma; a systematic review and meta-analysis of cohort and case-control studies. J Nephropharmacol. 2024;13(1):e11651. DOI: 10.34172/npj.2023.11651.

***Corresponding author**: Anna Ghorbani Doshantapeh, Email: annaghorbani1367@gmail.com

Meta-analysis

Introduction

Non-Hodgkin lymphoma is a prevalent form of hematological malignancy, constituting almost 90% of all lymphomas (1,2). Non-Hodgkin lymphomas encompass a diverse group of B-cell or T-cell neoplasms originating from lymphoid tissues and rank as the seventh most common cancer in Europe (3). Data from 2016–2020 indicate an annual incidence of 18.7 new cases of non-Hodgkin lymphoma per 100 000 individuals and a mortality rate of 5.1 per 100 000 individuals per year. In 2020, approximately 788 781 people were living with non-Hodgkin lymphoma in the United States (4). Diffuse large B-cell lymphoma is the most prevalent histological subtype within non-Hodgkin lymphomas, accounting for nearly 30% of all non-Hodgkin lymphoma cases in the United States, with an estimated 7 cases per 100 000 individuals annually (5,6).

Various pathogens, such as Epstein-Barr virus, helicobacter pylori, human T-cell lymphotropic virus-1, hepatitis C virus, and hepatitis B virus, have been connected with an increased susceptibility to non-Hodgkin lymphoma. In addition, the investigation of different medications, including oral contraceptives, hormone replacement therapy, anti-seizure drugs, and various steroids, has been undertaken in order to understand their relationship with non-Hodgkin lymphoma (7,8).

Type 2 diabetes is considered a risk parameters for various cancers (9,10). Epidemiological studies have demonstrated that diabetes prevalence is a risk factor for an increased occurrence of non-Hodgkin lymphoma in the general population (11,12). The immune system suppression, chronic inflammation, and lymphocyte dysfunction observed in individuals with diabetes are linked to the development of lymphoma, suggesting a plausible connection between diabetes and non-Hodgkin lymphoma (13).

Metformin, a commonly prescribed agent for lowering blood sugar levels, has shown potential anti-cancer properties (14). It is hypothesized that diabetes medications like metformin may have preventive effects on cancer. Epidemiological evidence has indicated a relationship between metformin and a reduced risk of various cancers, including overall and specific types (such as pancreatic and liver cancers) among diabetic patients (15). Nonetheless, the role of metformin in lymphoma remains unclear. It is uncertain whether metformin use decreases the risk of lymphoma or enhances treatment outcomes in lymphoma patients (16). Nevertheless, it appears that metformin treatment may inhibit the growth of B-cell and T-cell lymphoma by activating AMP-activated protein kinase and inhibiting the mechanistic target of rapamycin (mTOR) (17). Given the contradictory findings of prior investigations, our study undertook a comprehensive evaluation and meta-analysis to explore the plausible correlation between the utilization of metformin and the occurrence of non-Hodgkin lymphoma, thereby contributing novel insights to the current body of research.

Materials and Methods

Study design

This investigation involved a thorough evaluation and synthesis of existing research. It followed the recommended guidelines known as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (18). The study protocol was officially recorded on the website of the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42023469100.

Search strategy

The study conducted searches in various databases such as Scopus, PubMed, Web of Science, Cochrane, and Google Scholar up to September 20, 2023. Medical Subject Headings (MeSH) keywords were used, including Metformin, Metformin Hydrochloride, Glucophage, Lymphoma Non-Hodgkin, Reticulum Cell Sarcoma, Pleomorphic Lymphoma, and Undifferentiated Lymphoma. Boolean operators (AND, OR) were used to combine the keywords. The primary studies were also manually searched for eligibility. Below is an example of the search strategy used on the Web of Science website. An example of the search strategy on the Web of Science website is provided as follows: (Metformin OR Metformin Hydrochloride OR Glucophage) AND (Lymphoma, Non-Hodgkin OR Reticulum Cell Sarcoma OR Pleomorphic Lymphoma OR Undifferentiated Lymphoma).

Study inclusion criteria

Cohort and case-control studies exploring the association between the utilization of metformin and the occurrence of non-Hodgkin lymphoma were incorporated in the present investigation.

PICO components

- Population: Studies examining the correlation between metformin utilization and the occurrence of non-Hodgkin lymphoma.
- Intervention: Metformin use.
- Comparison: Non-diabetic individuals or diabetic individuals using anti-diabetic medications other than metformin.
- Outcomes: Probability of non-Hodgkin lymphoma.

Study exclusion criteria

Clinical trials, case reports, studies lacking access to the full-text, duplicate studies, studies reporting data qualitatively, studies of low quality, studies lacking necessary data for data analysis, and studies investigating the concurrent effects of metformin and another drug were excluded.

Quality assessment of studies

The evaluation of the studies under examination was conducted by utilizing the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) quality assessment checklist. This checklist encompasses a total of 22 inquiries, resulting in a final score that can range from 0 to 44A cutoff point of 16 was considered, and any study with a final score below 16 was excluded. After this stage, any discrepancies in responses to the checklist questions were reviewed, and a consensus between the two evaluators resolved any disagreements.

Data extraction

Two scholars autonomously gathered information from the research studies. The extracted data were recorded in a checklist, which included author names, year, country, study type, age group, comparison group, sample size, the odds ratio between metformin use and non-Hodgkin lymphoma, and its 95% confidence interval. A third scholar critically examined the data that was extracted by the two preceding researchers in order to resolve any inconsistencies.

Statistical analysis

The logarithm of the odds ratio (OR) was calculated for each study and used for combining the study results. To assess heterogeneity, the Cochrane Q test and I^2 index were conducted. Additional analyses, such as meta-regression and publication bias assessment, were conducted (20). Regarding the I^2 index, there are three categories of heterogeneity classification (21). Due to the presence of high heterogeneity (I^2=73.8%), the current study utilized a random-effects model. The data analysis was carried out employing STATA 14 software, while a significance level of $P<0.05$ was deemed significant.

Results

Study selection

After searching the mentioned databases, 98 articles were found. After reviewing titles, 31 duplicate articles were removed. The abstracts of the remaining 67 articles were examined, and out of this number, 6 articles were excluded due to a lack of access to their full texts. The full texts of the remaining 61 articles were reviewed, and 16 articles were excluded due to incomplete information required for data analysis. Ultimately, 45 articles remained, of which 39 were further excluded based on other exclusion criteria, leaving 6 articles for the systematic review and meta-analysis (Figure 1).

In this meta-analysis, six observational studies (five

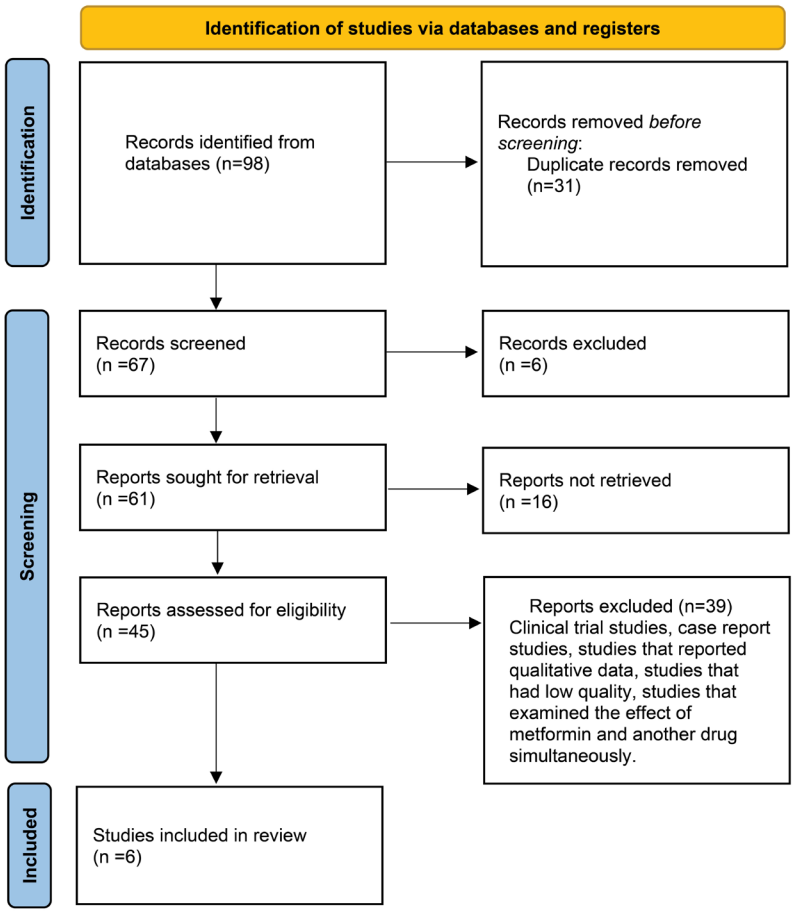

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Background information of the articles that entered the systematic review and meta-analysis process

First Author	Country	Type of study	Sample size	Mean age (y)	No. of people in metformin group	No. of people in compare group	Compare group	During the study period
Klil-Drori (22)	UK	Cohort	100343	>18	252	100091	Type 2 diabetes	Between 1998 and 2014
Wang (23)	USA	Cohort	149522	NR	1637	147885	Non diabetics/ untreated diabetes	NR
Tseng (24)	Taiwan	Cohort	196382	53-55	1076	195306	Non-metformin	Until December 31, 2011
Ye (25)	Canada	Case-control	5242	>40	878	4364	Type 2 diabetes	NR
Kautzky-Willer (26)	Austria	Cohort	1847051	50-60	NR	NR	NR	2006–2007
Gini (27)	Italy	Cohort	32247	40-84	NR	NR	Type 2 diabetes	2002–2009

NR: Not reported.

cohort studies and one case-control study) with a total of 2 330 787 participants were examined. The smallest study, Ye et al in 2018 (22), had 5242 participants, while the largest study, Kautzky-Willer et al in 2017 (23), included 1,847,051 participants. Other information on the studies under review is provided in Table 1.

Primary outcome

In Figure 2, the OR for the association between metformin use and non-Hodgkin lymphoma was estimated as OR = 0.91 (95% CI: 0.78, 1.07), indicating no statistically significant association between metformin administration and non-Hodgkin lymphoma.

In Figure 3, we utilized subgroup analysis to assess the odds ratio between metformin administration and non-Hodgkin lymphoma based on the type of study, and it revealed that these relationships were not statistically significant. The odds ratio between metformin use and

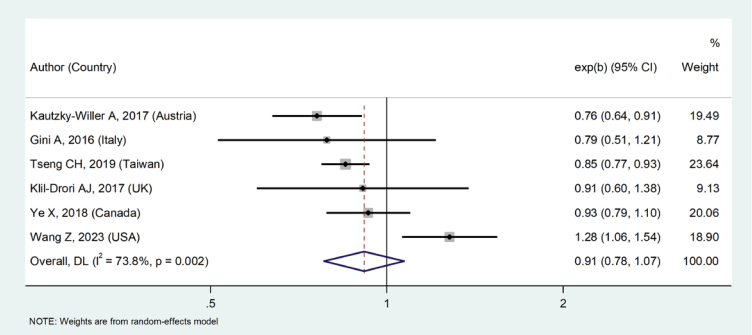

Figure 2. Forest plot of the association between metformin administration and non-Hodgkin lymphoma with its 95% confidence interval.

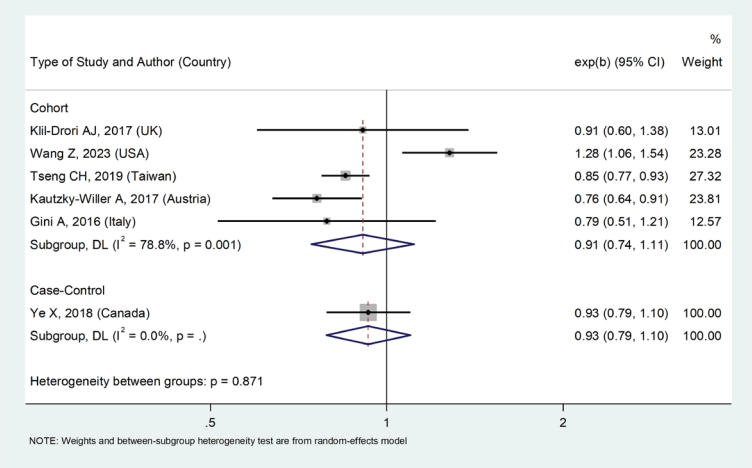

Figure 3. Forest plot of the association between metformin administration and non-Hodgkin lymphoma by type of studies with its 95% confidence interval.

non-Hodgkin lymphoma in cohort studies was OR = 0.91 (95% CI: 0.74, 1.11), and in the case-control study, it was OR = 0.93 (95% CI: 0.79, 1.10).

Secondary Outcomes

The secondary outcomes investigated in this meta-analysis were chronic lymphocytic leukemia/small lymphocytic leukemia and diffuse large B-cell lymphoma. The odds ratio between metformin use and chronic lymphocytic leukemia/small lymphocytic leukemia was OR = 0.93 (95% CI: 0.71, 1.21), and the odds ratio between metformin use and diffuse large B-cell lymphoma was OR = 1.06 (95% CI: 0.61, 1.83), with both relationships not being statistically significant.

In Figure 4, the meta-regression plot indicated a lack of statistically significant correlation between the impact of metformin usage on non-Hodgkin lymphoma and the variable representing the quantity of study samples ($P = 0.343$).

The results of the publication bias assessment, as shown in Figure 5, indicated no statistically significant publication bias ($P = 0.749$), signifying that the search phase was conducted thoroughly and without selective reporting, covering all relevant studies.

In Figure 6, the sensitivity analysis revealed that the study by Wang et al (23) in 2023 and the study by Kautzky-Willer et al (26) in 2017 had the most significant impact on the current study's results. Specifically, after removing the study by Wang et al, the final meta-analysis result changed to OR = -0.16 (95% CI: -0.23, -0.09), and with the exclusion of the study by Kautzky-Willer et al, the current study's result shifted to OR = -0.04 (95% CI: -0.22, 0.13).

Discussion

The results of our meta-analysis indicated that there was no discernible correlation between the utilization of metformin and the development of non-Hodgkin lymphoma, chronic lymphocytic leukemia/small lymphocytic leukemia, and diffuse large B-cell lymphoma. To be precise, the use of metformin did not have a substantial effect in diminishing the occurrence of non-Hodgkin lymphoma. The findings of the meta-analysis conducted by Zhang et al, encompassing a sample of 67 studies comprising a considerable cohort of 10,695,875 individuals diagnosed with type 2 diabetes, revealed a lower likelihood of cancer occurrence among those who utilized metformin in comparison to those who abstained from its usage (OR = 0.70, 95% CI = 0.65–0.76) (28). Based on the results of the meta-analysis by Ng and colleagues, which included 58 studies aimed at investigating the impact of metformin on colorectal adenoma and the incidence of colorectal cancer and oncological outcomes, metformin users, compared to users of non-metformin antidiabetic drugs, had a lower risk of colorectal adenoma (risk ratio [RR] = 0.77, 95% CI = 0.67–0.88), advanced adenoma (RR = 0.61, 95% CI = 0.42–0.88), and colorectal cancer (RR = 0.76, 95% CI = 0.69–0.84) (29). In a meta-analysis conducted by Yao et al on 13 studies with the aim of assessing the correlation between lung neoplasm and metformin in patients with type 2 diabetes, the results showed that metformin users had a lower risk of lung neoplasm compared to non-metformin users (RR = 0.89, 95% CI = 0.83–0.96) (30). The results of the meta-analysis by Shuai and colleagues which included 11 cohort

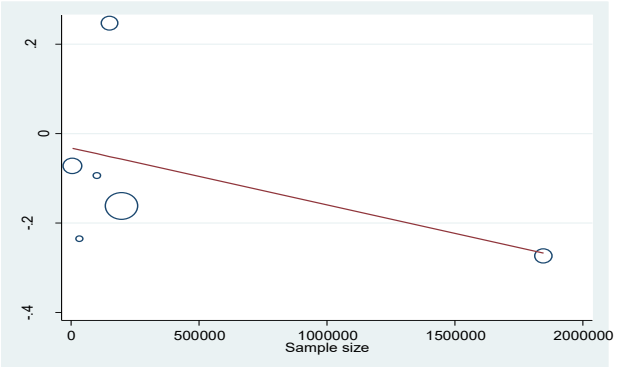

Figure 4. Meta-regression plot of association between metformin use and non-Hodgkin lymphoma by sample size studies.

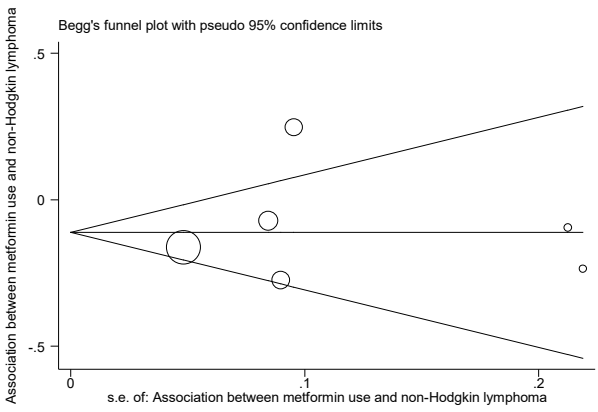

Figure 5. Publication bias detected by funnel plot.

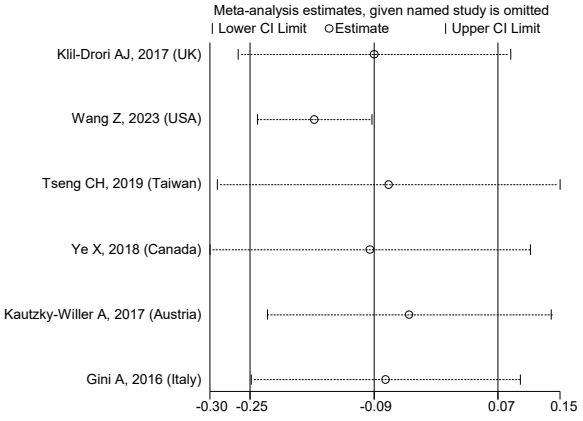

Figure 6. Sensitivity analysis.

studies conducted to the impact of metformin on gastric carcinoma in patients with type 2 diabetes, showed that metformin administration was associated with a 21% reduction in the occurrence of gastric carcinoma (HR = 0.79, 95% CI = 0.62–1) (31). In the meta-analysis conducted by Hu and colleagues (2023), involving 29 studies with the aim of investigating the link between the utilization of metformin and the probability of pancreatic cancer in individuals diagnosed with type 2 diabetes, the researchers demonstrated that, compared to not using metformin, the utilization of metformin may potentially lower the likelihood of developing pancreatic cancer in individuals diagnosed with type 2 diabetes (OR = 0.82, 95% CI = 0.69-0.98) (32). The results of these studies did not align with the findings of the present research because, in our meta-analysis, we concluded that metformin had no effect on reducing the occurrence of non-Hodgkin lymphoma. However, in the studies mentioned, it is observed that individuals who used metformin had a lower likelihood of developing pancreatic, stomach, lung, and colorectal cancers compared to those who did not use metformin.

In a meta-analysis carried out by Wu et al encompassing five cohort studies and case-control studies, the findings indicated that the utilization of metformin did not exhibit the potential to diminish the likelihood of developing gallbladder cancer among individuals diagnosed with type 2 diabetes (HR = 0.88, 95% CI = 0.60–1.28) (33). In a study conducted by Lu et al, a meta-analysis was carried out to examine the association between the utilization of metformin and the likelihood of developing breast cancer in females. The findings of the study indicated that the utilization of metformin did not result in a reduction in the relative risk of breast cancer in females when compared to the usage of alternative anti-diabetic medications (RR = 0.82, 95% CI = 0.60–1.12) (34). In a separate meta-analysis performed by Wang et al, encompassing a total of 18 cohort studies and 6 case-control studies involving 2 009 504 male patients diagnosed with type 2 diabetes, the findings revealed that the utilization of metformin did not exhibit a reduction in the combined risk of prostate cancer. This observation remained consistent across both case-control studies (HR = 0.97, 95% CI = 0.84–1.12) and cohort studies (HR = 0.94, 95% CI = 0.79–1.12) (35). The results of these studies were in line with the conclusion of our meta-analysis because, in these previous studies, researchers found that metformin could not reduce the risk of developing liver, breast, or prostate tumor. In our meta-analysis, we also concluded that metformin use in individuals who had used metformin did not reduce the likelihood of non-Hodgkin lymphoma compared to those who had not used metformin.

Conclusion

The findings of the present meta-analysis demonstrate that metformin does not yield a substantial impact on the prevalence of non-Hodgkin lymphoma, chronic lymphocytic leukemia/small lymphocytic leukemia, and diffuse large B-cell lymphoma. However, considering the aforementioned limitations and the limited number of studies, it appears that more research studies are needed and should be published to reduce substantial heterogeneity and bias for a more definitive conclusion.

Limitations of study

This study had several limitations, including the limited number of studies, non-uniform distribution of studies between the two study types (cohort and case-control), overlapping age ranges reported in the studies that did not allow for subgroup analysis based on patients' age, missing information on metformin dosage and duration of use in the studies examined, and a lack of data stratified by gender in the studies. Therefore, it was not possible to compare the results between women and men in this meta-analysis. It is recommended that future research endeavors address these limitations.

Acknowledgments

The authors would like to thank Hamid Nasri and Diana Sarokhani for guidance and editing of manuscript registration on the PROSPERO website and Guissu Research Corporation (Hossein Mardanparvar) for guidance and editing of manuscript registration on the Research Registry website.

Authors' contribution

Conceptualization: Anna Ghorbani Doshantapeh and Razieh Bagheri Shahzadeh Aliakbari.
Data curation: Sina Salati and Anna Ghorbani Doshantapeh.
Formal analysis: Navid Asgari and Nasim Zaman Samghabadi.
Investigation: Elnaz Ataei and Sara Abbasian.
Methodology: Navid Asgari and Farshad Gharebakhshi
Project management: Anna Ghorbani Doshantapeh.
Resources: All authors.
Supervision: Elnaz Ataei.
Validation: Elnaz Ataei and Mohammad Akbari.
Visualization: Razieh Bagheri Shahzadeh Aliakbari.
Writing–original draft: Anna Ghorbani Doshantapeh, Razieh Bagheri Shahzadeh Aliakbari, Navid Asgari, Farshad Gharebakhshi, Mohammad Akbari, and Nasim Zaman Samghabadi.
Writing–reviewing and editing: Elnaz Ataei, Sina Salati, and Sara Abbasian.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website with (ID: CRD42023469100) and Research Registry website

(UIN reviewregistry1721). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support
None.

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