**MATERIALS AND METHODS**

**Search strategies**

Highly sensitive electronic search was conducted from four databases, including the PubMed, Scopus, and Embase (update to January 28, 2023) with no language restriction.

**The search strategy on PubMed**

( ( "uric acid" [Title/Abstract] OR urate [Title/Abstract] OR purine [Title/Abstract] OR hyperuricemia [Title/Abstract] OR gout [Title/Abstract] ) OR (antioxidant [Title/Abstract] AND ( "uric acid" OR urate OR purine OR hyperuricemia OR gout) ) ) AND ( "Periodontal Diseases" [MeSH Terms] OR periodontitis NOT "apical periodontitis" ) AND ( blood [Title/Abstract] OR serum [Title/Abstract] OR plasma [Title/Abstract] OR circulation [Title/Abstract] OR GCF [Title/Abstract] OR "gingival crevicular fluid" [Title/Abstract] OR saliva [Title/Abstract] )

**The search strategy on SCOPUS**

( TITLE-ABS-KEY ( blood OR serum OR plasma OR circulation OR gcf OR "gingival crevicular fluid" OR saliva ) AND DOCTYPE ( ar ) ) AND ( ( ( ALL ( "uric acid" OR urate OR purine OR hyperuricemia OR gout ) AND TITLE-ABS-KEY ( antioxidant ) ) AND DOCTYPE ( ar ) ) OR ( TITLE-ABS-KEY ( "uric acid" OR urate OR purine OR hyperuricemia OR gout ) AND DOCTYPE ( ar ) ) ) AND ( ( TITLE-ABS-KEY ( "periodontal disease" ) OR TITLE-ABS-KEY ( periodontitis ) AND NOT TITLE-ABS-KEY ( "apical periodontitis" ) ) AND DOCTYPE ( ar ) )

**The search strategy on EMBASE**

( 'uric acid':ti,ab,kw OR urate:ti,ab,kw OR purine:ti,ab,kw OR hyperuricemia:ti,ab,kw OR gout:ti,ab,kw ) OR ( ( 'uric acid' OR urate OR purine OR hyperuricemia OR gout ) AND antioxidant:ti,ab,kw ) AND ( ( 'periodontal disease':ti,ab,kw OR periodontitis:ti,ab,kw ) NOT 'apical periodontitis':ti,ab,kw ) AND ( blood:ti,ab,kw OR serum:ti,ab,kw OR plasma:ti,ab,kw OR circulation:ti,ab,kw OR gcf:ti,ab,kw OR 'gingival crevicular fluid':ti,ab,kw OR saliva:ti,ab,kw )

**The search strategy on Web of Science**

( "uric acid" OR urate OR purine OR hyperuricemia OR gout ) AND ( "periodontal disease" OR periodontitis NOT "apical periodontitis" ) AND ( blood OR serum OR plasma OR circulation OR gcf OR "gingival crevicular fluid" OR saliva )

**TABLES**

**Table S1.** The characteristics of excluded studies.

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Year** | **Type of study** | **Reasons for exclusion** |
| Almerich-Silla, J M. et al. | 2015 | Cross-sectional study | Not involving uric acid |
| Al-Rawi, N H. et al. | 2017 | Case-control study | Participants with unclear/barred systemic condition |
| Arora, N. et al. | 2013 | Randomized controlled trials study | Lack of periodontal health controls |
| Babaei, H. et al. | 2018 | Randomized controlled trials study | Lack of periodontal health controls |
| Barnes, V M. et al. | 2014 | Cross-sectional study | Not involving uric acid |
| Barnes, V M. et al. | 2009 | Case-control study | Lack of periodontal health controls |
| Batista, E L. et al. | 2010 | Interventional study | Lack of periodontal health controls |
| Botelho, J. et al. | 2020 | Retrospective cohort study | Participants with unclear/barred systemic condition |
| Byun, S H. et al. | 2020 | Cross-sectional study | Lack of periodontal health controls |
| Cao, Y. et al. | 2016 | Cross-sectional study | Participants with unclear/barred systemic condition |
| Chapple, I L C. et al. | 2007 | Prospective cohort study | Lack of periodontal health controls |
| Chapple, I L C. et al. | 1997 | Cross-sectional study | Lack of periodontal health controls |
| Chen, H W. et al. | 2018 | Cross-sectional study | Not involving uric acid |
| Choromańska, M. et al. | 2017 | Case-control study | Participants with unclear/barred systemic condition |
| Fons-Badal, C. et al. | 2019 | Randomized controlled trials study | Lack of periodontal health controls |
| Fornasaro, S. et al. | 2021 | Case-control study | Not involving uric acid |
| Front, E. et al. | 2013 | Interventional study | Lack of periodontal health controls |
| Garg, N. et al. | 2006 | Case-control study | Lack of periodontal health controls |
| Greabu, M. et al. | 2006 | Interventional study | Lack of periodontal health controls |
| Gümüş, P. et al. | 2009 | Case-control study | Lack of periodontal health controls |
| Gumus, P. et al. | 2015 | Case-control study | Not involving uric acid |
| Khodaii, Z. et al. | 2019 | Case-control study | Full text unavailable |
| Konopka, T. et al. | 2007 | Case-control study | Not involving uric acid |
| Lee, C. et al. | 2018 | Prospective cohort study | Lack of periodontal health controls |
| Mashayekhi, F. et al. | 2005 | Case-control study | Not involving uric acid |
| Miricescu, D. et al. | 2011 | Case-control study | Duplicate publication |
| Moore, S. et al. | 1994 | Case-control study | Participants with unclear/barred systemic condition |
| Mourāo, L C. et al. | 2014 | Randomized controlled trials study | Lack of periodontal health controls |
| Munther, S | 2019 | Cross-sectional study | Lack of periodontal health controls |
| Nguyen, T T. et al. | 2017 | Case-control study | Not involving uric acid |
| Novaković, N. et al. | 2013 | Interventional study | Duplicate publication |
| Olszewska-Czyz, I. et al. | 2022 | Cross-sectional study | Lack of periodontal health controls |
| Pulido-Moran, M. et al. | 2017 | Cross-sectional study | Participants with unclear/barred systemic condition |
| Rai, B. et al. | 2011 | Interventional study | Lack of periodontal health controls |
| Sculley, D V. et al. | 2003 | Prospective cohort study | Participants with unclear/barred systemic condition |
| Seydanur et al. | 2019 | Randomized controlled trials study | Lack of periodontal health controls |
| Sezer, U. et al. | 2016 | Case-control study | Not involving uric acid |
| Shetty, M S. et al. | 2018 | Case-control study | Participants with unclear/barred systemic condition |
| Shetty, M. et al. | 2012 | Case-control study | Full text unavailable |
| Sincar, C D. et al. | 2017 | Case-control study | Lack of periodontal health controls |
| Su, H. et al. | 2009 | Cross-sectional study | Not involving uric acid |
| Summers, C J. et al. | 1968 | Cross-sectional study | Lack of periodontal health controls |
| Tamaki, N. et al. | 2015 | Cross-sectional study | Not involving uric acid |
| Tartaglia, G M. et al. | 2017 | Cross-sectional study | Lack of periodontal health controls |
| Hu, S A. et al. | 2022 | Cross-sectional study | Lack of periodontal health controls |
| Chabuk, M I. et al. | 2021 | Case-control study | Lack of periodontal health controls |
| Tu, Y K. et al. | 2013 | Prospective cohort study | Participants with unclear/barred systemic condition |
| Vernerov, A. et al. | 2021 | Case-control study | Lack of periodontal health controls |
| Yoshino, F. et al. | 2012 | Cross-sectional study | Not involving uric acid |
| Ziebolz, D. et al. | 2007 | Cross-sectional study | Participants with unclear/barred systemic condition |
| Zipkin, I. et al. | 1964 | Case-control study | Participants with unclear/barred systemic condition |
| Chen, S., et al., | 2023 | Case-control study | Not involving uric acid |
| Toczewska, J., et al., | 2022 | Case-control study | Not involving uric acid |

**Table S2.** Quality assessment of the included case-control studies with Newcastle-Ottawa Scale.

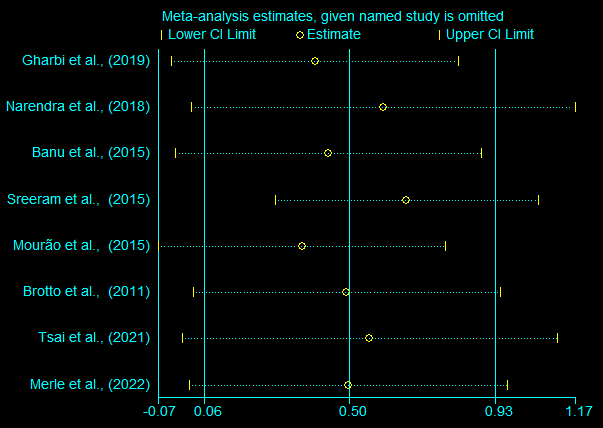
|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Studies | Selection | | | | | Comparability | | Exposure | | | Final Score |
| **Is the case definition adequate?** | | **Representativeness of the cases?** | **Selection of controls** | **Definition of controls** | **Comparability of cases and controls on the basis of the design or analysis** | | **Ascertainment of exposure** | **Same method of ascertainment for cases and controls** | **Non-response rate** |
| **Main factor**† | **Additional factor**‡ |
| Gharbi et al., 2019 | | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Sakanaka et al., 2017 | | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 6 |
| Banu et al., 2015 | | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Diab-Ladki et al., 2003 | | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 2 |
| Mourão et al., 2015 | | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| Mathur et al., 2013 | | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 4 |
| Brotto et al., 2011 | | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 6 |
| Fatima G et al., 2016 | | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Senouci et al., 2021 | | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 8 |
| Novakovic et al., 2014 | | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Priya, K.L., et al., 2022 | | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 |

†, Gender was selected as the main factor; ‡, Age was considered as an additional factor.

**Table S3**. Agency for Healthcare Research and Quality for risk of bias assessment of the cross-sectional studies.

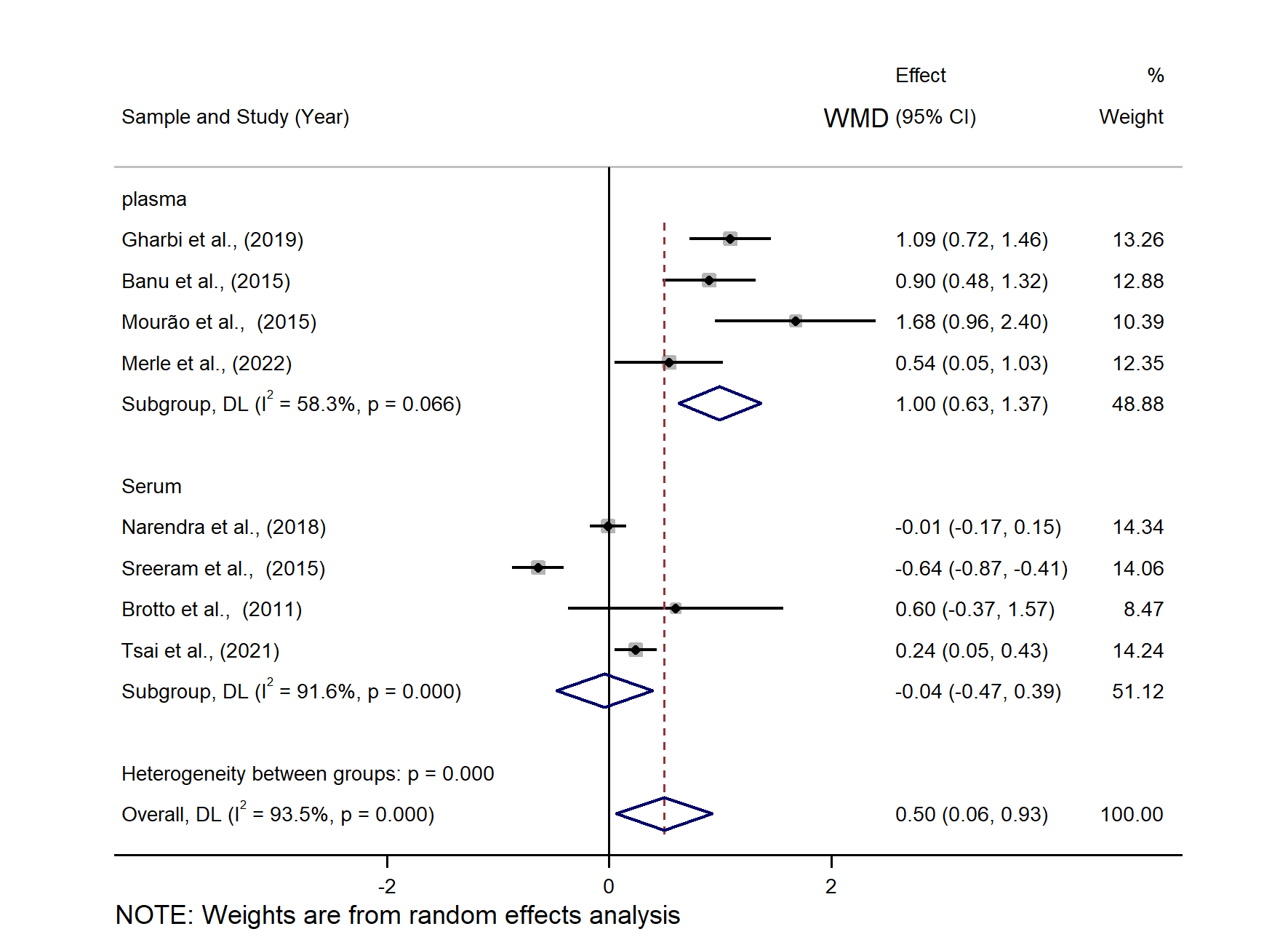
|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Narendra et al., 2018** | **Miricescu et al., 2014** | **Sreeram et al., 2015** | **Sharma et al., 2018** | **Tsai et al., 2021** | **Merle, C.L., et al., 2022** |
| **Define the source of information** | Yes | Yes | Yes | Yes | Yes | Yes |
| **List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications** | Yes | No | Yes | Yes | Yes | Yes |
| **Indicate time period used for identifying patients** | No | No | Yes | No | Yes | Yes |
| **Indicate whether or not subjects were consecutive if not population-based** | No | Yes | Yes | Yes | No | Yes |
| **Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants** | Yes | Yes | Yes | Yes | Yes | Yes |
| **Describe any assessments undertaken for quality assurance purposes** | No | No | No | No | No | No |
| **Explain any patient exclusions from analysis** | Yes | No | Yes | Yes | Yes | Yes |
| **Describe how confouding was assessed and/or controlled** | Yes | No | No | Yes | Yes | Yes |
| **If applicable, explain how missing data were handled in the analysis** | No | No | No | No | No | Yes |
| **Summarize patient response rates and completeness of data collection** | Yes | Yes | Yes | Yes | Yes | Yes |
| **Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data of follow-up was obtained** | No | No | No | No | No | No |
| **Total score** | 6 | 4 | 7 | 7 | 7 | 9 |

**FIGURES**

****

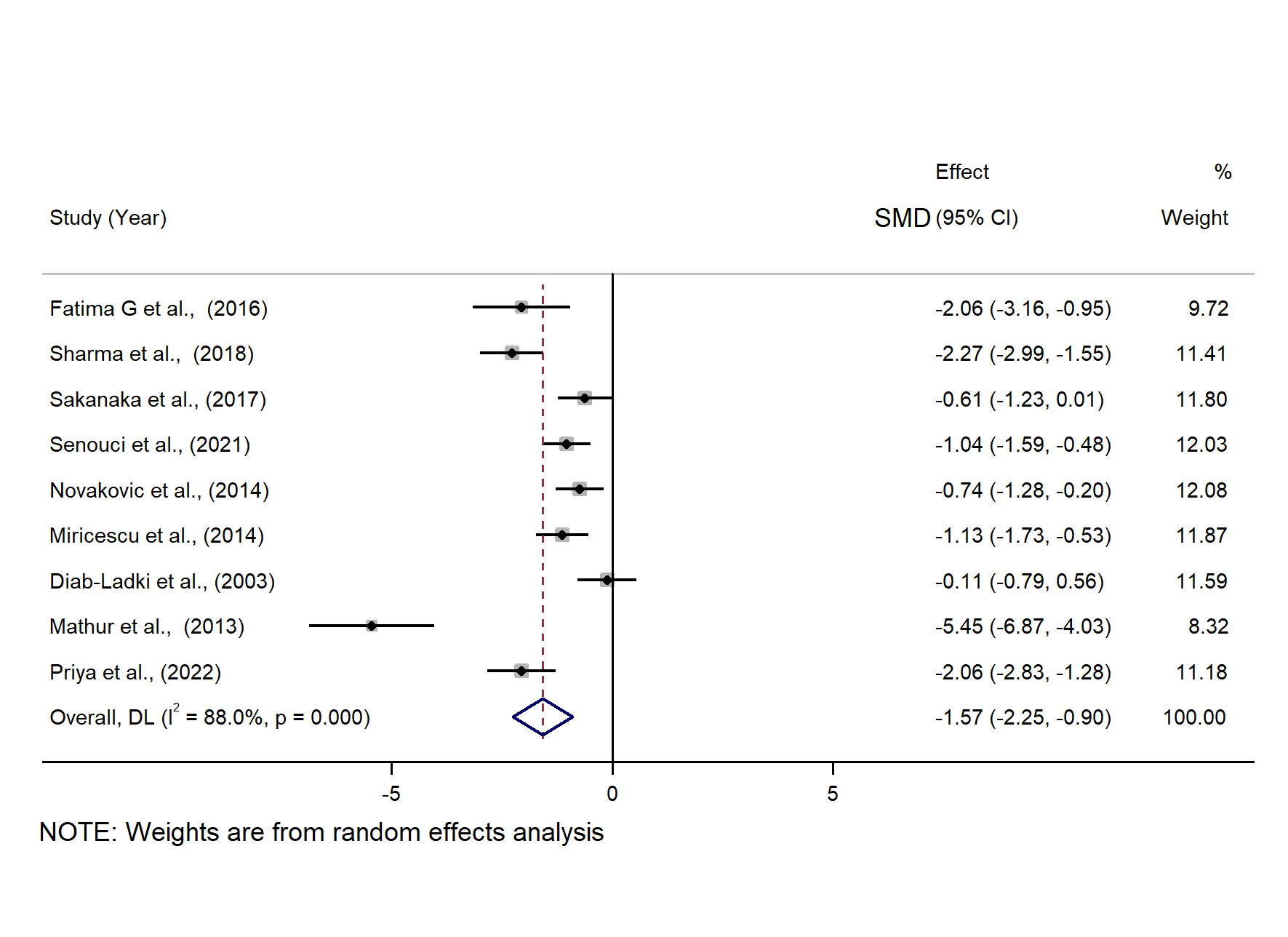
**Figure S1.** Sensitivity analysis of the relationship between periodontitis and controls of UA levels in blood.

In these studies, no clearly heterogeneous origin could be found.

****

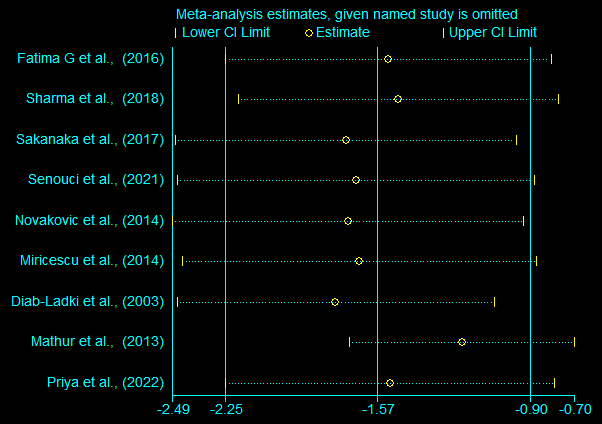
**Figure S2.** Forest plot comparing UA levels of periodontitis vs. control in plasma/serum subgroups.

*CI,* confidence interval; *WMD*, weighted mean difference.

****

**Figure S3.** Forest plot comparing the salivary UA levels of periodontitis vs control before sensitivity analysis.

There was a high heterogeneity among the studies (*I*2 = 88.6%, *P* < 0.001). Therefore, sensitivity analysis should be performed to find sources of heterogeneity. *SMD*, standardized mean difference.

****

**Figure S4.** Sensitivity analysis of the relationship between periodontitis and controls of UA levels in saliva.

A sensitivity analysis was performed to explore potential sources of heterogeneity. Statistical heterogeneity was decreased obviously, indicating that they were likely the source of heterogeneity.