

## **APPENDIX 1.** Search strategy.

Search terms were checked against each database vocabulary list and exploded as required.

Additional text words were added to identify previous indexing for new subject terms. Our search covered all languages (with an English abstract), original trials or reviews of trials, on human subjects, either in full text, conference proceeding, or abstract. The search strategy in MEDLINE is listed below:

1. Lupus Nephritis/ or (Lupus Erythematosus, Systemic/ and (Nephritis/ or Glomerulonephritis/)) or (lupus adj10 nephritis).ti,ab.
2. cyclophosphamide/ or ifosfamide/ or (ifofosfamide or "nsc-109724" or "nsc-109 724" or nsc109724 or "asta z 4942" or "asta z4942" or astaz4942 or iphosphamide or "iso endoxan" or holoxan or cyclophosphamide or cytophosphan or cytoxan or "b-518" or b518 or neosar or "nsc-26271" or nsc26271 or procytox or endoxan or cyclophosphane or sendoxan).mp. or Azathioprine/ or (azathioprine or imurel or immuran or imuran or azathioprine or azothioprine).mp. or Mycophenolic Acid/ or (mycophenolic or mofetil).mp. or methylprednisolone/ or prednisone/ or (prednisone or dehydrocortisone or encorton or predniment or kortancyl or enkortolon or decortisyl or rectodelt or meticorten or encortone or dacortin or "predni tablinen" or cortancyl or sone or panafcort or "delta-cortisone" or deltacortisone or cortan or METHYLPREDNISOLONE or METIPRED or medrol or urbason).mp. or DEXAMETHASONE/ or (DEXAMETHASONE or millicorten or maxidex or decaspray or dexpak or dexasone or oradexon or hexadecadrol or decaject or methylfluorprednisolone or decameth or PREDNISOLONE or diadresonf or predate or predonine or "di adreson f").mp. or glucocorticoids/ or dexamethasone/ or prednisolone/ or

tacrolimus/ or (tacrolimus or "fk 506" or "anhydrous tacrolimus" or prograf or fr900506 or "fujisawa brand of tacrolimus" or "janssen brand of tacrolimus" or "fr-900506" or "cilag brand of tacrolimus" or prograf or "fr 900506" or "fk-506" or fk506 or "tacrolimus, anhydrous").mp.

3. ("clinical trial, all" or clinical trial).pt. or clinical trials as topic/ or clinical trial, phase i.pt. or clinical trials, phase i as topic/ or clinical trial, phase ii.pt. or clinical trials, phase ii as topic/ or clinical trial, phase iii.pt. or clinical trials, phase iii as topic/ or clinical trial, phase iv.pt. or clinical trials, phase iv as topic/ or controlled clinical trial.pt. or controlled clinical trials as topic/ or randomized controlled trial.pt. or randomized controlled trials as topic/ or (((singl\* or doubl\* or trebl\* or tripl\*) adj5 (mask\* or blind\*)) or (placebo\* or random\*) or (latin adj square)).mp. or comparative study/ or (control\* or prospective\* or volunteer\*).mp or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or case-control studies/ or retrospective studies/ or cross-sectional studies/ or meta-analysis.pt. or meta-analysis as topic/ or multicenter study.pt. or multicenter studies as topic/

4. 1 and 2 and 3

## **APPENDIX 2.** Prior assumptions.

Incorporating prior belief or knowledge into analysis is a distinctive trait of Bayesian analysis by which more information is used. Quantifying the educated subjective (or “active”) prior belief forms the ground for the informative prior assumption. We performed the analyses under 2 sets of prior assumptions. First, under a minimum of prior assumptions, an analysis was undertaken using a flat or noninformative prior distribution (which is therefore an objective look at the results based on data alone):

$$\begin{aligned}\mu_{sb} &\sim N(0, 100^2) \\ d_t &\sim N(0, 100^2)\end{aligned}$$

with  $d_1 = 0$  as an anchor point.

Second, a skeptical analysis was undertaken using an informative prior distribution expressing a subjective belief that there is no difference between any pair of immunosuppressive agents in inducing renal remission at 6 months<sup>28</sup>. A normal prior distribution on the log odds parameter was used for this purpose, which is a precise distribution centred at the null, with its precision calculated by mapping the relative treatment effect up to the minimal clinically meaningful OR of 2 (empirically chosen), measured in logarithmic scale. Therefore, the interval between  $OR = \pm 2$  covers 1.96 SE units of the logarithmic distribution on both sides:

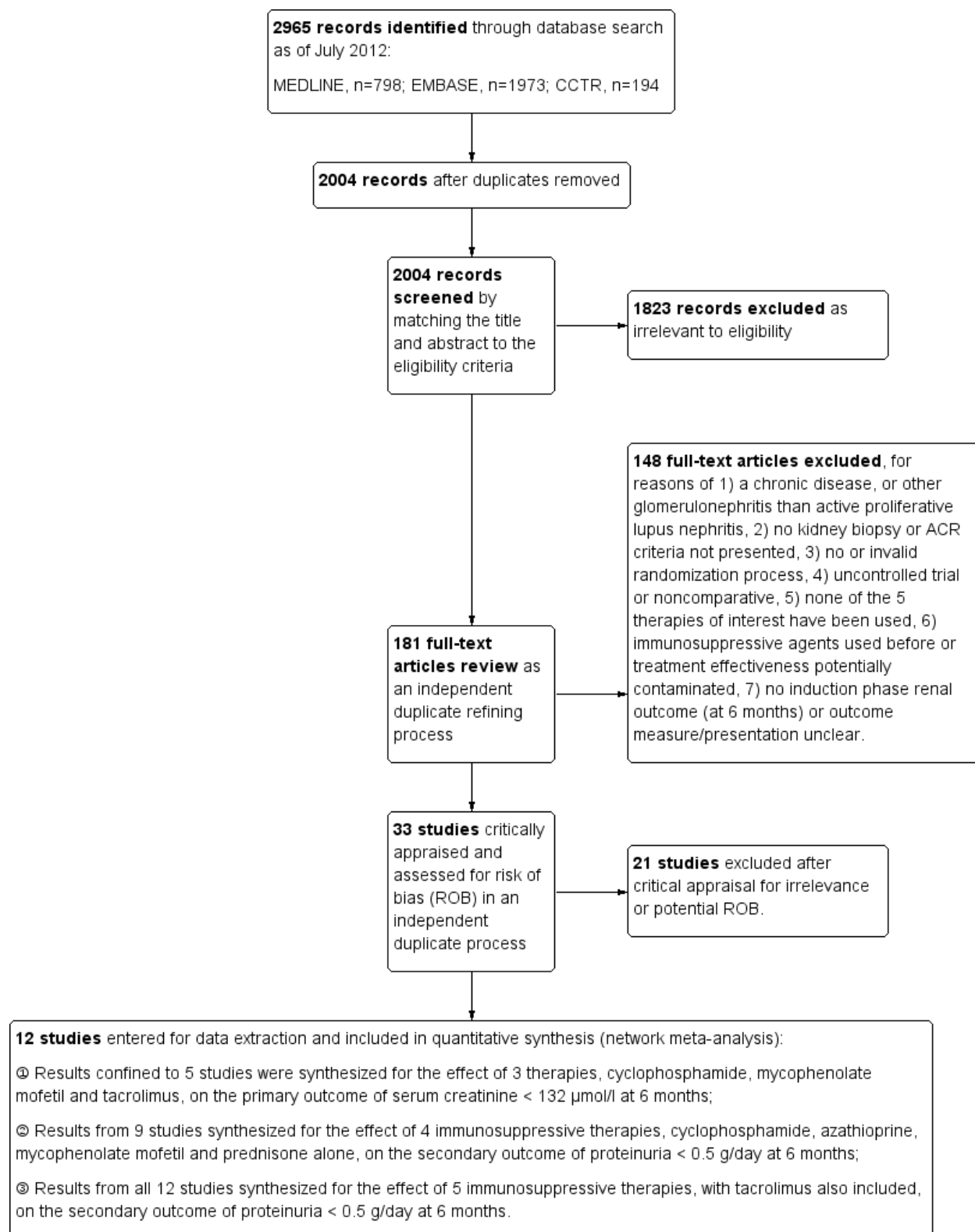
$$\begin{aligned}\log(OR = 2) &= 0.6931 \\ SE_{\log(OR)} &= \frac{0.6931 - 0}{1.96} \\ &= 0.3536\end{aligned}$$

therefore, the skeptical prior distribution is specified as:

$$\begin{aligned}\mu_{sb} &\sim N(0, 0.3536^2) \\ d_t &\sim N(0, 0.3536^2)\end{aligned}$$

Different sets of initial values for the stochastic nodes were used to further examine the robustness of results.

### APPENDIX 3. Flow chart of the literature search.



#### APPENDIX 4. Reasons for excluding 21 studies on critical appraisal.

Study	Reasons for exclusion
Bao H et al. 2008 [40] (China, northern)	Purely membranous LN studied, or mixed with Class IV
Boletis JN et al. 1999 [41] (Greece)	Not randomized at the induction phase, immunoglobulin not used in any of the other studies
Boumpas DT et al. 1992 [42] (NIH)	No complete renal remission data at 6 months
Cade R et al. 1973 [43] (Florida)	A special outcome measure used, patients allocated in an alternate fashion but no information given about allocation concealment
Doria A et al. 1994 [44] (Italy)	Comparison of plasmapheresis vs. methylprednisolone out of scope of interest for this review; azathioprine used in all three arms
Dyadyk A et al. 2001 [45] (Ukraine)	No time given for the response
El-Sehemy MS et al. 2006 [8] (Egypt)	Purely membranous LN studied with PLN, immunosuppressive therapies received previously and response failed, no complete renal remission data at 6 months
Houssiau FA et al. 2010 [46] (MAINTAIN)	A 12 week trial of induction treatment, < 6 months; no complete renal remission data
Hu W et al. 2002 [47] (China, eastern)	Cyclophosphamide received previously in both arms with no favourable response achieved, mycophenolate mofetil compared with control that is out of scope of interest for this review
Klippel JH et al. 1978 [48] (NIH)	Outcome measure cannot be used for this analysis (two special measures of treatment failure)
Mok CC et al. 2010 [49]	Purely membranous LN studied with mixed Classes III/V,

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(Hong Kong)	IV/V; complete response combined with partial response data
Mok CC et al. 2005 [50]	Not randomized and uncontrolled
(Hong Kong)	
Nakamura T et al. 2002 [51]	Immunosuppressive therapies received previously and response failed
(Japan)	
Petri M et al. 2010 [52]	Cyclophosphamide high dose vs. low dose out of scope of interest for this review
(Johns Hopkins)	
Steinberg AD et al. 1971 [53] (NIH)	A 10 week trial of induction treatment, < 6 months
Steinberg AD and Decker JL 1974 [33] (NIH)	A 10 week trial of induction treatment, < 6 months
Sundel RP and Lisk L 2008 [54]	No complete renal remission data
(ALMS)	
Wallace DJ et al. 1998 [55]	Plasmapheresis unlinked to any of the other studies; cyclophosphamide used in both arms
(UCLA)	
Wang J et al. 2007 [56]	A different disease than the others (Class IV LN with non-inflammatory necrotizing vasculopathy) studied, potentially posing a selection bias
(China, eastern)	
Zavada J et al. 2010 [57]	A 9 month trial of induction treatment, > 6 months
(Czech)	
Zeher M et al. 2011 [58]	Prednisone standard vs. reduced dose, out of scope of interest for this review
(Hungary)	

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Abbreviations: LN: lupus nephritis; PLN: proliferative lupus nephritis.

## REFERENCES:

- [40] H. Bao, Z. H. Liu, H. L. Xie, W. X. Hu, H. T. Zhang, L. S. Li, Successful treatment of class V+IV lupus nephritis with multitarget therapy, *Journal of the American Society of Nephrology* 19 (2008) 2001–2010.
- [41] J. N. Boletis, J. Ioannidis, K. A. Boki, H. M. Moutsopoulos, Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis, *The Lancet* 354 (1999) 569–570.

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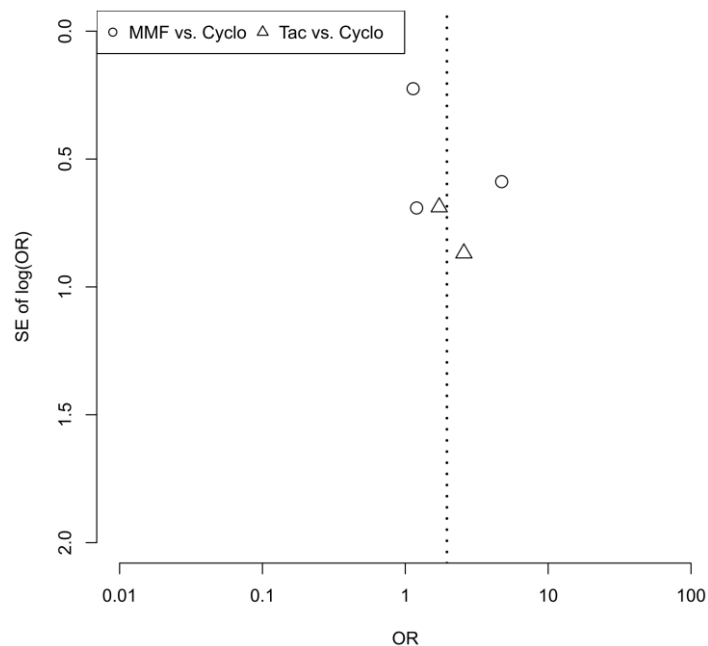
- [42] D. T. Boumpas, H. A. Austin, J. E. Balow, E. M. Vaughan, C. H. Yarboro, J. H. Klippel, A. D. Steinberg, Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis, *The Lancet* 340 (1992) 741–745.
- [43] R. Cade, G. Spooner, E. Schlein, M. Pickering, A. De Quesada, A. Holcomb, L. Juncos, G. Richard, D. Shires, D. Levin, et al., Comparison of azathioprine, prednisone, and heparin alone or combined in treating lupus nephritis, *Nephron* 10 (1973) 37–56.
- [44] A. Doria, A. Piccoli, P. Vesco, E. Vaccaro, P. Marson, G. De Silvestro, E. Ossi, P. Gambari, Therapy of lupus nephritis. A two-year prospective study [conference proceeding], in: *Annales de médecine interne*, volume 145, pp. 307–311.
- [45] A. Dyadyk, I. Vasilenko, A. Bagriy, O. Dyadyk, N. Yarovaya, Y. Roschin, L. Kholopov, Azathioprine and cyclophosphamide in treatment of patients with diffuse proliferative lupus nephritis - a randomized controlled study [CCTR abstract], *Nephrology Dialysis Transplantation* 16 (2001) A57.
- [46] F. A. Houssiau, D. D'Cruz, S. Sangle, P. Remy, C. Vasconcelos, R. Petrovic, C. Fiehn, E. de Ramon Garrido, I. M. Gilboe, M. Tektonidou, et al., Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: Results from the MAINTAIN nephritis trial, *Annals of the Rheumatic Diseases* 69 (2010) 2083–2089.
- [47] W. Hu, Z. Liu, H. Chen, Z. Tang, Q. Wang, K. Shen, L. Li, et al., Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis, *Chinese Medical Journal, English Edition*, Beijing 115 (2002) 705–709.
- [48] J. H. Klippel, A. D. Steinberg, J. L. Balow, P. H. Plotz, J. L. Decker, Randomized study of intravenous cyclophosphamide (IVCY) and cyclophosphamide plus azathioprine (CY + AZ) in lupus nephritis [CCTR abstract], *Arthritis & Rheumatism* 21 (1978) 570.
- [49] C. C. Mok, S. Ying, C. W. Yim, W. L. Ng, Tacrolimus (Tac) versus mycophenolate mofetil (MMF) for the treatment of membranous lupus nephritis: A randomized controlled trial [conference proceeding], *Lupus* 19 (2010) 16.

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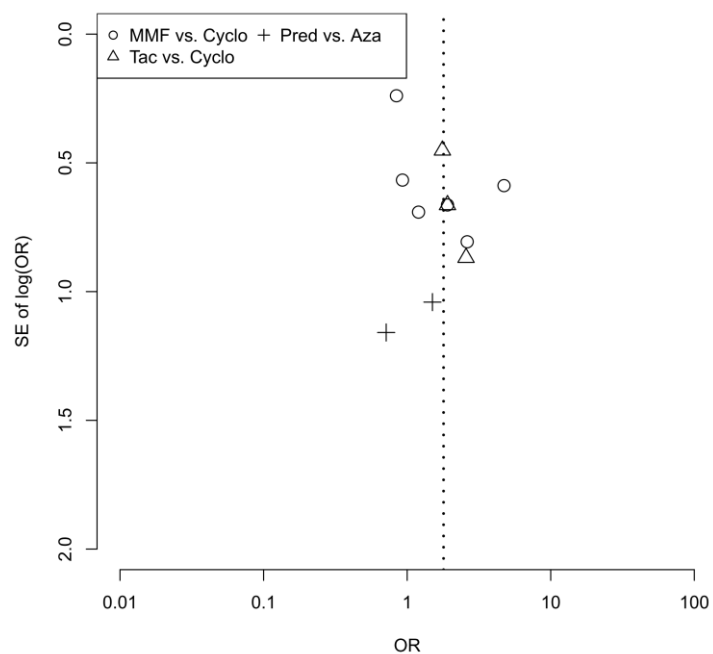
- [50] C. H. I. C. Mok, K. A. H. Tong, C. H. I. H. To, Y. U. I. P. Siu, T. A. K. C. Au, Tacrolimus for induction therapy of diffuse proliferative lupus nephritis: An open-labeled pilot study, *Kidney International* 68 (2005) 813–817.
- [51] T. Nakamura, C. Ushiyama, M. Hara, S. Osada, K. Ugai, N. Shimada, K. Hayashi, I. Ebihara, H. Koide, Comparative effects of plasmapheresis and intravenous cyclophosphamide on urinary podocyte excretion in patients with proliferative lupus nephritis, *Clinical Nephrology* 57 (2002) 108–113.
- [52] M. Petri, R. A. Brodsky, R. J. Jones, D. Gladstone, M. Fillius, L. S. Magder, High-dose cyclophosphamide versus monthly intravenous cyclophosphamide for systemic lupus erythematosus: A prospective randomized trial, *Arthritis & Rheumatism* 62 (2010) 1487–1493.
- [53] A. D. Steinberg, H. B. Kaltreider, P. J. Staples, E. J. Goetzl, N. Talal, J. L. Decker, Cyclophosphamide in lupus nephritis: A controlled trial, *Annals of Internal Medicine* 75 (1971) 165–171.
- [54] R. P. Sundel, L. Lisk, Mycophenolate mofetil compared with intravenous cyclophosphamide as induction treatment for pediatric lupus nephritis: A randomized trial, *Arthritis & Rheumatism* 58 (2008) S632–S633.
- [55] D. J. Wallace, D. Goldfinger, S. H. Pepkowitz, M. Fichman, A. L. Metzger, J. O. Schroeder, H. H. Euler, Randomized controlled trial of pulse/synchronization cyclophosphamide/apheresis for proliferative lupus nephritis, *Journal of Clinical Apheresis* 13 (1998) 163–166.
- [56] J. Wang, W. Hu, H. Xie, H. Zhang, H. Chen, C. Zeng, Z. Liu, L. Li, Induction therapies for class iv lupus nephritis with non-inflammatory necrotizing vasculopathy: Mycophenolate mofetil or intravenous cyclophosphamide, *Lupus* 16 (2007) 707–712.
- [57] J. Zavada, S. S. Pešickova, R. Ryšava, M. Olejarova, P. Horák, Z. Hrnčíř, I. Rychlík, M. Havrda, J. Vítova, J. Lukáč, et al., Cyclosporine a or intravenous cyclophosphamide for lupus nephritis: The Cyclofa-Lune study, *Lupus* 19 (2010) 1281–1289.
- [58] M. Zeher, A. Doria, J. Lan, G. Aroca, D. Jayne, I. Boletis, F. Hiepe, H. Prestele, P. Bernhardt, Z. Amoura, Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis, *Lupus* 20 (2011) 1484–1493.

**APPENDIX 5.** Funnel plots for detecting publication bias.

A.



B.

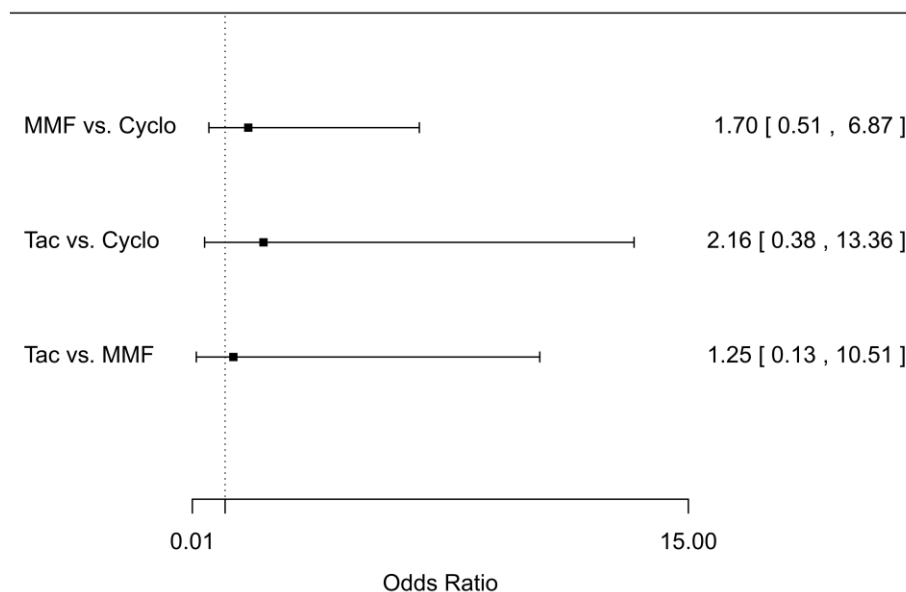


Funnel plots of all studies with Cyclo as a basic comparator. A. The top part plots 2 comparisons for the outcome of serum creatinine < 132  $\mu$ mol/l: MMF vs. Cyclo (circles, 3 studies), Tac vs.

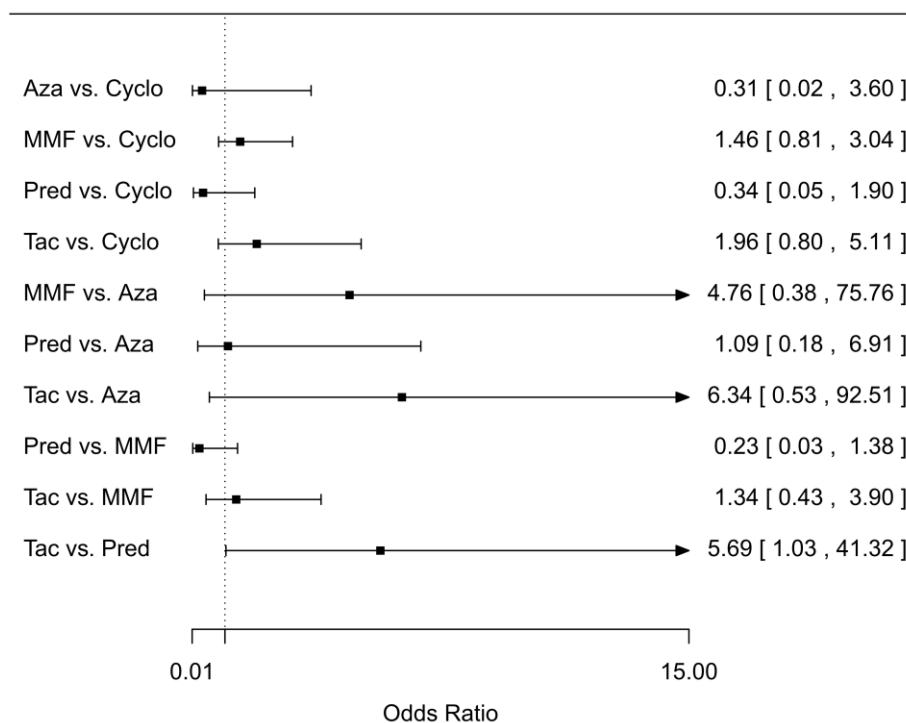
Cyclo (triangles, 2 studies); it shows that published data in general may favor MMF or Tac against Cyclo, but all clustered to the null effect ( $OR = 1$ ), especially for a larger sample size (when the standard error is small). B. The bottom part plots 3 comparisons for the outcome of proteinuria  $< 0.5$  g/day, which are MMF vs. Cyclo (circles, 6 studies), Tac vs. Cyclo (triangles, 3 studies) and prednisone alone vs. Aza (pluses, 2 studies); it shows that published data in general may favor MMF or Tac against Cyclo, but all clustered to the null effect, especially for a larger sample size. Aza: azathioprine; Cyclo: cyclophosphamide; MMF: mycophenolate mofetil; Tac: tacrolimus; Pred: prednisone alone.

**APPENDIX 6.** Caterpillar plots of the Bayesian network metaanalysis.

A.



B.



Caterpillar plots of the Bayesian network metaanalysis (see also Table 3). A. Serum creatinine remission. B. Proteinuric remission. OR of renal remission at 6 months associated with each of the pairwise comparisons between immunosuppressive agents. The dotted line indicates  $OR = 1$ . Aza: azathioprine; Cyclo: cyclophosphamide; MMF: mycophenolate mofetil; Tac: tacrolimus; Pred: prednisone alone.