National Institute for Health and Care Excellence

FINAL

Hypertension in Pregnancy

[G] Evidence review for assessment of proteinuria

NICE guideline NG133

Evidence reviews

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These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Review question: How effective are spot protein/creatinine ratio or albumin/creatinine ratio measurements as compared with a 24 hour urine collection for the identification of proteinuria in women with hypertensive disorders of pregnancy?

Introduction

The reliable detection of significant proteinuria is important in women with new-onset hypertension during pregnancy because it helps distinguish between those pregnancies with pre-eclampsia and those with gestational hypertension and this determines the pathways for future monitoring and management.

Traditionally proteinuria has been assessed initially by urine dipstick (which can be read visually or by an automated device) and confirmed by various methods of laboratory quantification either using spot samples of urine, or 24 hour urine collection. A 24 hour urine collection is a time-consuming procedure for the woman, and in recent years spot urinary protein:creatinine ratio (PCR) and spot urinary albumin:creatinine ratio (ACR) (which are widely used outside maternity services) have been increasingly used in pregnant women. International definitions have recommended certain thresholds of PCR and ACR for diagnosis of 'significant proteinuria', and which are included in definitions of pre-eclampsia.

The aim of this review is to determine the best method for assessing proteinuria and to determine if currently used thresholds of PCR and ACR are correct to diagnose significant proteinuria.

Summary of the protocol

See Table 1 for a summary of the Population, Index test, Reference test, and Outcome (PIRO) characteristics of this review.

Table 1: Summary of the protocol (PIRO table)

Population	Pregnant women with hypertension. This population includes women with: • chronic hypertension • gestational hypertension • suspected pre-eclampsia
Index test	• Spot albumin:creatinine ratio (ACR) • Spot protein:creatinine ratio (PCR)
Reference test	• Urinary protein excretion of ≥300mg in 24 hours
Outcome	**Critical outcomes** • Sensitivity • Negative likelihood ratio **Important outcomes** • Area under the curve (AUC) • Positive likelihood ratio • Specificity

ACR: albumin:creatinine ratio; AUC: area under the curve; mg: milligrammes; PCR: protein:creatinine ratio;

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declaration of interests were recorded according to NICE's 2018 conflicts of interest policy (see Register of interests).

Included studies reported data for ACR in mg/mmol only. Study data for PCR was reported as mg/mmol, mg/mg, mg/g, mg/dL, mg, and presented without units. We made the pragmatic decision to transform the data for direct comparison using the approximate conversion factor, for example, PCR 0.30 (ratio without units) = PCR 0.30 mg/mg = PCR 30mg/mmol = PCR of 300mg/g. Data are presented here to 2 decimal places only (as a ratio), and in whole numbers when converted back into mg/mmol.

Following conversion to a ratio, meta-analysis was performed when at least 4 different studies reported data at the same cut-off threshold. This was possible at PCR cut-off points 0.15, 0.19, 0.20, 0.30, 0.40, and 0.45 only.

Sub-group analyses were only possible at PCR 0.30, where 4 studies (Bhatti 2018, Kyle 2008, Leanos-Miranda 2007, Mohseni 2013) excluded spot urine samples taken at the first morning void. The remaining 6 studies reporting at PCR 0.30 included samples taken at the first morning void (though not exclusively first void), or did not report this (second subgroup analysis: Amin 2015, Durnwald 2003, Lamontagne 2014, Saudan 1997, Waugh 2017, Wilkinson 2013).

Imprecision was assessed according to pre-specified thresholds for sensitivity (a critical outcome measure), which were identified by the guideline committee as representing clinically meaningful results. Sensitivity of ≥90% was regarded as high, and ≥75% was regarded as moderate.

Clinical evidence

Included studies

Twenty-three studies were included in this review.

Four studies were retrospective cohort studies (Al 2004, Park 2013, Rodriguez-Thompson 2001, Stout 2013), 17 were prospective cohort studies (Amin 2015, Bhatti 2018, Durnwald 2003, Dwyer 2008, Kucukgoz Gulec 2017, Kyle 2008, Lamontagne 2014, Leanos-Miranda 2007, Mohseni 2013, Rizk 2007, Saudan 1997, Tun 2012, Valdes 2016, Waugh 2005, Waugh 2017, Wheeler 2007, Wilkinson 2013), 1 descriptive cohort study (Nisar 2017) and 1 case-series (Eslamian 2011).

Four studies reported on the diagnostic accuracy of ACR (Kyle 2008, Waugh 2005, Waugh 2017, Wilkinson 2013), and 22 studies reported on the diagnostic accuracy of PCR (Al 2004, Amin 2015, Bhatti 2018, Durnwald 2003, Dwyer 2008, Eslamian 2011, Kucokgoz-Gulec 2017, Lamontagne 2014, Leanos-Miranda 2007, Mohseni 2013, Nisar 2017, Park 2013, Rizk 2007, Rodriguez-Thompson 2001, Saudan 1997, Stout 2013, Tun 2012, Valdes 2016, Waugh 2017, Wheeler 2007, Wilkinson 2013),

One study (Mohseni 2013) presented data for spot/random samples collected at two time points (10am and 4pm) related to the same 24 hour collection. To avoid double counting, we took the decision to use only the data presented for the 10am sample as these reported more conservative estimates for diagnostic accuracy (consistently lower sensitivity at each cut-off).

One study (Waugh 2017) performed multiple analyses for PCR based on the different assays performed at the local laboratory, or central study laboratory using two different assays (BZC assay and PGR assay). To reflect clinical practice, we have used results from the local laboratory PCR analysis for inclusion in this review. Assays for ACR were conducted at the central laboratory only, therefore these data were included in the review.

See the literature search strategy in appendix B and clinical evidence study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Index / Reference tests	Outcomes
Al 2004 Turkey Retrospective	N=185 New onset hypertension in late pregnancy	Random PCR (excluded 1st morning void) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity
Amin 2015 India Prospective	N=102 Hypertension after 20wks	Random PCR (unclear void time – not mentioned in study) *compared to* 24 hour urine collection	• Sensitivity • Specificity • LR+ • LR-
Bhatti 2018 UK Prospective	N=476 Attending antenatal hypertension clinic	Random PCR (excluded 1st morning void) *compared to* 24 hour urine collection	• Sensitivity • Specificity
Durnwald 2003 USA Prospective	N=220 Suspected PE after 24wks	Random PCR (unclear void time – not mentioned in study) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity
Dwyer 2008 USA Prospective	N=116 Suspected PE	Spot PCR (unclear void time – not mentioned in study) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity
Eslamian 2011 Iran Case series	N=100 New onset hypertension after 20wks	Spot PCR (excluded 1st morning void) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity
Kucukgoz Gulec 2017	N=205 Suspected PE in late pregnancy	Spot PCR (unclear void time – not mentioned in study) *compared to*	• AUC • Sensitivity • Specificity

Study	Population	Index / Reference tests	Outcomes
Turkey Prospective		24 hour urine collection	
Kyle 2008 New Zealand Prospective	N=150 Attending high risk antenatal clinic after 20wks	Spot PCR and spot ACR (excluded 1st morning void) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity • LR+ • LR-
Lamontagne 2014 Canada Prospective	N=91 Indication for a 24hr sample to test for PE in 2nd or 3rd trimester	Random PCR (included 1st morning void) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity • LR+ • LR-
Leanos-Miranda 2007 Mexico Prospective	N=927 New onset hypertension after 20wks	Random PCR (excluded 1st morning void) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity • LR+ • LR-
Mohseni 2013 Iran Prospective	N=66 New onset hypertension after 20wks, and underwent 24hr collection	Random PCR (excluded 1st morning void) *compared to* 24 hour urine collection	• AUC • DTA 2x2 table • Sensitivity • Specificity
Nisar 2017 India Descriptive	N=404 Hypertension after 20wks	Spot PCR (unclear void time – not mentioned in study) *compared to* 24 hour urine collection	• DTA 2x2 table • Sensitivity • Specificity
Park 2013 South Korea Retrospective	N=46 Symptoms of PE with one clinical indication	Random PCR (unclear void time – not mentioned in study) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity
Rizk 2007 United Arab Emirates Prospective	N=51 Attended hospital for management of hypertension	Spot PCR (excluded 1st morning void) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity • LR+ • LR-
Rodriguez-Thompson 2001 USA Retrospective	N=138 Had both PCR and 24hr collection	Random PCR (excluded 1st morning void) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity
Saudan 1997 Australia	N=100 Admitted to hospital for	Spot PCR (unclear void – “in the morning”) *compared to*	• Sensitivity • Specificity

Study	Population	Index / Reference tests	Outcomes
Prospective	management of hypertensive disorders	24 hour urine collection	
Stout 2013 USA Retrospective	N=356 Suspected PE after 20wks	Random PCR (unclear void time – not mentioned in study) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity • LR+ • LR-
Tun 2012 USA Prospective	N=90 Undergoing 24hr collection for suspected PE after 20wks	Spot PCR (unclear void time – not mentioned in study) *compared to* 24 hour urine collection	• Sensitivity • Specificity
Valdes 2016 Chile Prospective	N=72 Diagnosed with pregnancy hypertensive disorder after 20wks	Random PCR (unclear void time – not mentioned in study) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity
Waugh 2005 UK Prospective	N=171 New onset hypertension after 20wks	Spot ACR (measured using DCA2000 analyzer) (only used 1st morning void) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity • LR+ • LR-
Waugh 2017 UK Prospective	N=959 New onset hypertension after 20wks	Spot PCR and spot ACR (unclear void time – not mentioned in study) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity • LR+ • LR-
Wheeler 2007 USA Prospective	N=126 New or worsening hypertension after 20wks	Spot PCR (excluded 1st morning void) *compared to* 24 hour urine collection	• AUC • Sensitivity • Specificity
Wilkinson 2013 Ireland Prospective	N=132 (from 89 women) Suspected PE after 20wks	Spot PCR and spot ACR (included 1st morning void) *compared to* 24 hour urine collection	• Sensitivity • Specificity

ACR: albumin:creatinine ratio; AUC: area under the curve; DTA: diagnostic test accuracy; hr: hour; LR+: positive likelihood ratio; LR-: negative likelihood ratio; PCR: protein:creatinine ratio; PE: pre-eclampsia;; wks: weeks;

See appendix D for the clinical evidence tables, appendix E for the Forest plots, and appendix M for a graphical representation of the data (scatter plots showing results for sensitivity and specificity by cut-off threshold).

Quality assessment of clinical outcomes included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation

The committee were aware of an economic analysis conducted as part of a large, UK-based study (Waugh 2017). However this study was not included in the economic evidence review because it assessed the cost-effectiveness of strategies to diagnose severe pre-eclampsia rather than the diagnosis of proteinuria.

Evidence statements

Spot albumin:creatinine ratio (ACR) for the identification of significant proteinuria (≥300mg/24 hours)

Cut-off threshold: 1.0 mg/mmol

- One cohort study (N=132 samples from 89 women) provided moderate quality evidence to show very high sensitivity and low specificity when using an ACR cut-off point of 1.0 mg/mmol to identify significant proteinuria. Likelihood ratios show this is not a useful test when the test is positive, but is a very useful test when negative.

Cut-off threshold: 1.5 mg/mmol

- One cohort study (N=132 samples from 89 women) provided low quality evidence to show very high sensitivity and low specificity when using an ACR cut-off point of 1.5 mg/mmol to identify significant proteinuria. Likelihood ratios show this is not a useful test when the test is positive, but is a very useful test when negative.

Cut-off threshold: 2.0 mg/mmol

- Meta-analysis of 4 cohort studies (N=1412) provided very low quality evidence to show very high sensitivity and low specificity when using an ACR cut-off point of 2.0 mg/mmol to identify significant proteinuria. Likelihood ratios show this is not a useful test when the test is positive, but is a very useful test when negative.

Cut-off threshold: 2.5 mg/mmol

- One cohort study (N=132 samples from 89 women) provided low quality evidence to show very high sensitivity and moderate specificity when using an ACR cut-off point of 2.5 mg/mmol to identify significant proteinuria. Likelihood ratios show this is not a useful test when the test is positive, but is a very useful test when negative.

Cut-off threshold: 3.0 mg/mmol

- One cohort study (N=132 samples from 89 women) provided low quality evidence to show high sensitivity and moderate specificity when using an ACR cut-off point of 3.0 mg/mmol to identify significant proteinuria. Likelihood ratios show this is not a useful test when the test is positive, and a moderately useful test when negative.

Cut-off threshold: 3.5 mg/mmol

- One cohort study (N=150) provided low quality evidence to show very high sensitivity and moderate specificity when using an ACR cut-off point of 3.5 mg/mmol to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when the test is positive, and a very useful test when negative.
- A second cohort study (N=132 samples from 89 women) provided low quality evidence to show high sensitivity and moderate specificity when using an ACR cut-off point of 3.5 mg/mmol to identify significant proteinuria. Likelihood ratios show this is not a useful test when the test is positive, and a moderately useful test when negative.

Cut-off threshold: 8.0 mg/mmol

- One cohort study (N=150) provided low quality evidence to show very high sensitivity and very high specificity when using an ACR cut-off point of 8.0 mg/mmol to identify significant proteinuria. Likelihood ratios show this is a very useful test when the test is positive, and a very useful test when negative.

Spot protein:creatinine ratio (PCR) for the diagnosis of significant proteinuria (≥300mg/24 hours)

Cut-off threshold: 0.08 (~8mg/mmol)

- One cohort study (N=356) provided high quality evidence to show very high sensitivity and very low specificity when using a PCR cut-off point of 0.08 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive or negative.

Cut-off threshold: 0.10 (~10mg/mmol)

- One cohort study (N=132) provided moderate quality evidence to show very high sensitivity and very low specificity when using a PCR cut-off point of 0.10 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive, but is very useful when negative (LR- not calculable due to sensitivity=1.00).

Cut-off threshold: 0.12 (~12mg/mmol)

- One cohort study (N=356) provided moderate quality evidence to show high sensitivity and very low specificity when using a PCR cut-off point of 0.12 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive or negative.

Cut-off threshold: 0.13 (~13mg/mmol)

- One cohort study (N=185) provided moderate quality evidence to show high sensitivity and low specificity when using a PCR cut-off point of 0.13 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive, and is moderately useful when the result is negative.

Cut-off threshold: 0.14 (~14mg/mmol)

- One cohort study (N=138) provided high quality evidence to show very high sensitivity and low specificity when using a PCR cut-off point of 0.14 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive, but is very useful when negative (LR- not calculable due to sensitivity=1.00).

Cut-off threshold: 0.15 (~15mg/mmol)

- Meta-analysis of 5 cohort studies (N=696) provided low quality evidence to show very high sensitivity and low specificity when using a PCR cut-off point of 0.15 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive, but is very useful when negative.

Cut-off threshold: 0.16 (~16mg/mmol)

- One cohort study (N=138) provided high quality evidence to show very high sensitivity and low specificity when using a PCR cut-off point of 0.16 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive, but is very useful when negative.

Cut-off threshold: 0.17 (~17mg/mmol)

- One cohort study (N=138) provided moderate quality evidence to show high sensitivity and low specificity when using a PCR cut-off point of 0.16 to identify significant

proteinuria. Likelihood ratios show this is not a useful test when the result is positive, but is very useful when negative.

Cut-off threshold: 0.18 (~18mg/mmol)

- One cohort study (N=185) provided low quality evidence to show moderate sensitivity and low specificity when using a PCR cut-off point of 0.18 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive or negative.
- A second cohort study (N=138) provided moderate quality evidence to show high sensitivity and low specificity when using a PCR cut-off point of 0.18 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive, but is moderately useful when negative.

Cut-off threshold: 0.19 (~19mg/mmol)

- Meta-analysis of 5 cohort studies (N=878) provided moderate quality evidence to show moderate sensitivity and low specificity when using a PCR cut-off point of 0.19 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive or negative.

Cut-off threshold: 0.20 (~20mg/mmol)

- Meta-analysis of 6 cohort studies (N=1179) provided very low quality evidence to show high sensitivity and low specificity when using a PCR cut-off point of 0.20 to identify significant proteinuria. Likelihood ratios show this is not a useful test when the result is positive, but is moderately useful when negative.

Cut-off threshold: 0.21 (~21mg/mmol)

- One cohort study (N=476) provided moderate quality evidence to show moderate sensitivity and moderate specificity when using a PCR cut-off point of 0.21 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when the result is positive or negative.
- Two cohort studies (not meta-analysed: N=138, N=126) provided moderate quality evidence to show moderate sensitivity and moderate specificity when using a PCR cut-off point of 0.21 to identify significant proteinuria. Likelihood ratios show this is not a useful test when positive, but is moderately useful when negative.

Cut-off threshold: 0.22 (~22mg/mmol)

- One cohort study (N=100) provided low quality evidence to show moderate sensitivity and high specificity when using a PCR cut-off point of 0.22 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive, and moderately useful when negative.

Cut-off threshold: 0.25 (~25mg/mmol)

- One cohort study (N=100) provided low quality evidence to show very high sensitivity and moderate specificity when using a PCR cut-off point of 0.25 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when positive, and very useful when negative.
- One cohort study (N=132) provided low quality evidence to show moderate sensitivity and high specificity when using a PCR cut-off point of 0.25 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive, and moderately useful when negative.

Cut-off threshold: 0.28 (~28mg/mmol)

- One cohort study (N=116) provided moderate quality evidence to show low sensitivity and very high specificity when using a PCR cut-off point of 0.28 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive, but not a useful test when negative.

- One cohort study (N=205) provided high quality evidence to show moderate sensitivity and low specificity when using a PCR cut-off point of 0.28 to identify significant proteinuria. Likelihood ratios show this is not a useful test when positive or negative.

Cut-off threshold: 0.30 (~30mg/mmol)

- Meta-analysis of 10 cohort studies (N=3224) provided very low quality evidence to show high sensitivity and high specificity when using a PCR cut-off point of 0.30 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when positive and negative.
- Sub-group analysis for 4 cohort studies which excluded the 1st morning urine void (N=1620) provided very low quality evidence to show high sensitivity and very high specificity when using a PCR cut-off point of 0.30 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive and negative
- Sub-group analysis for 6 cohort studies which included first morning urine samples, or did not specify that these samples were excluded, (N=1604) provided very low quality evidence to show moderate sensitivity and moderate specificity when using a PCR cut-off point of 0.30 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when positive and negative.

Cut-off threshold: 0.35 (~35mg/mmol)

- One cohort study (N=67) provided moderate quality evidence to show high sensitivity and low specificity when using a PCR cut-off point of 0.35 to identify significant proteinuria. Likelihood ratios show this is not a useful test when positive, but is very useful when negative.
- A second cohort study (N=100) provided low quality evidence to show moderate sensitivity and very high specificity when using a PCR cut-off point of 0.35 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive and moderately useful when negative.

Cut-off threshold: 0.36 (~36mg/mmol)

- One cohort study (N=83) provided moderate quality evidence to show low sensitivity and moderate specificity when using a PCR cut-off point of 0.36 to identify significant proteinuria. Likelihood ratios show this is not a useful test when positive or negative.
- A second cohort study (N=72) provided moderate quality evidence to show low sensitivity and high specificity when using a PCR cut-off point of 0.36 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when positive, but not useful when negative.

Cut-off threshold: 0.39 (~39mg/mmol)

- One cohort study (N=220) provided moderate quality evidence to show low sensitivity and low specificity when using a PCR cut-off point of 0.39 to identify significant proteinuria. Likelihood ratios show this is not a useful test when positive or negative.

Cut-off threshold: 0.40 (~40mg/mmol)

- Meta-analysis of 4 cohort studies (N=743) provided very low quality evidence to show low sensitivity and moderate specificity when using a PCR cut-off point of 0.40 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when positive, but not a useful test when negative.

Cut-off threshold: 0.45 (~45mg/mmol)

- Meta-analysis of 4 cohort studies (N=625) provided very low quality evidence to show low sensitivity and very high specificity when using a PCR cut-off point of 0.45 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive, but not a useful test when negative.

Cut-off threshold: 0.49 (~49mg/mmol)

- One cohort study (N=185) provided moderate quality evidence to show low sensitivity and moderate specificity when using a PCR cut-off point of 0.49 to identify significant proteinuria. Likelihood ratios show this is not a useful test when positive or negative.

Cut-off threshold: 0.50 (~50mg/mmol)

- One cohort study (N=67) provided low quality evidence to show moderate sensitivity and moderate specificity when using a PCR cut-off point of 0.50 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when positive and negative.
- A second cohort study (N=220) provided high quality evidence to show low sensitivity and moderate specificity when using a PCR cut-off point of 0.50 to identify significant proteinuria. Likelihood ratios show this is not a useful test when positive or negative.

Cut-off threshold: 0.53 (~53mg/mmol)

- One cohort study (N=205) provided moderate quality evidence to show moderate sensitivity and high specificity when using a PCR cut-off point of 0.53 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive, and moderately useful when negative.

Cut-off threshold: 0.55 (~55mg/mmol)

- One cohort study (N=67) provided low quality evidence to show moderate sensitivity and moderate specificity when using a PCR cut-off point of 0.55 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when positive and negative.
- A second cohort study (N=83) provided high quality evidence to show low sensitivity and moderate specificity when using a PCR cut-off point of 0.55 to identify significant proteinuria. Likelihood ratios show this not a useful test when positive or negative.

Cut-off threshold: 0.60 (~60mg/mmol)

- One cohort study (N=66) provided moderate quality evidence to show high sensitivity and very high specificity when using a PCR cut-off point of 0.595 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive and negative.
- A second cohort study (N=67) provided low quality evidence to show moderate sensitivity and moderate specificity when using a PCR cut-off point of 0.599 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when positive and when negative.
- A third cohort study (N=102) provided moderate quality evidence to show moderate sensitivity and moderate specificity when using a PCR cut-off point of 0.60 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when positive, but not a useful test when negative.

Cut-off threshold: 0.63 (~63mg/mmol)

- One cohort study (N=46) provided low quality evidence to show moderate sensitivity and very high specificity when using a PCR cut-off point of 0.63 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive (LR+ not calculable due to specificity=1.00) and moderately useful when negative.

Cut-off threshold: 0.75 (~75mg/mmol)

- One cohort study (N=102) provided moderate quality evidence to show low sensitivity and very high specificity when using a PCR cut-off point of 0.75 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive (LR+ not calculable due to specificity=1.00), but not a useful test when negative.

Cut-off threshold: 0.86 (~86mg/mmol)

- One cohort study (N=83) provided high quality evidence to show very low sensitivity and high specificity when using a PCR cut-off point of 0.86 to identify significant proteinuria. Likelihood ratios show this is a moderately useful test when positive, but is not a useful test when negative.

Cut-off threshold: 0.90 (~90mg/mmol)

- One cohort study (N=102) provided high quality evidence to show low sensitivity and very high specificity when using a PCR cut-off point of 0.90 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive (LR+ not calculable due to specificity=1.00), but not a useful test when negative.

Cut-off threshold: 1.19 (~119mg/mmol)

- One cohort study (N=356) provided high quality evidence to show very low sensitivity and very high specificity when using a PCR cut-off point of 1.19 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive, but is not a useful test when negative.

Cut-off threshold: 1.40 (~140mg/mmol)

- One cohort study (N=83) provided high quality evidence to show very low sensitivity and very high specificity when using a PCR cut-off point of 1.40 to identify significant proteinuria. Likelihood ratios show this is a very useful test when positive, but is not a useful test when negative.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Sensitivity and negative likelihood ratio were prioritised over specificity and positive likelihood ratio in this review. The main priority in testing for proteinuria is to ensure that women who may have pre-eclampsia are identified, to allow for appropriate monitoring and/or management. Therefore the priority is to ensure that a test detects these women (sensitivity). Whilst false positives may mean that women undergo unnecessary follow up, this is less of a concern than missing women who may need altered surveillance or intervention.

The quality of the evidence

Albumin:creatinine ratio (ACR)

Limited evidence from 4 cohort studies was classed as very low to moderate quality evidence. There was no serious risk of bias across any of the included studies: often not all women recruited/enrolled in the study were included in the analysis, but reasons for exclusion were well documented and valid (incomplete 24 hour urine collection, gave birth during 24 hour collection period, documented urine infection, refused consent/willingness to participate), and judged to have no to low impact on the risk of bias.

Individual studies were downgraded due to imprecision with wide confidence intervals (based on the critical outcome of sensitivity). Where studies could be pooled, the evidence was downgraded due to very high heterogeneity (assessed using the I^2 statistic). However, it was noted that heterogeneity is often extremely high with diagnostic accuracy studies, and therefore this downgrading of the evidence should be interpreted with caution. Only one cut-off threshold had sufficient data for meta-analysis (2.0 mg/mmol). The remaining cut-off points reported were from individual studies that each reported at multiple thresholds.

Protein:creatinine ratio (PCR)

The quality of the evidence ranged from very low to high. There was no serious risk of bias across any of the included studies: often not all women recruited/enrolled in the study were included in the analysis, but reasons for exclusion were well documented and valid (incomplete 24 hour urine collection, gave birth during 24 hour collection period, documented urine infection, refused consent/willingness to participate), and judged to have no to low impact on the risk of bias.

Individual studies were downgraded for imprecision with wide confidence intervals (based on the critical outcome of sensitivity). Where studies could be pooled, evidence was often downgraded due to very high heterogeneity (assessed using the I^2 statistic). However, it was noted that heterogeneity is often extremely high with diagnostic accuracy studies, and therefore this downgrading of the evidence should be interpreted with caution. When subgrouping was possible (at cut-off threshold PCR 30mg/mmol), heterogeneity remained very high within each subgroup.

Multiple cut-off thresholds were reported, with individual studies often reporting more than one threshold each. Studies reported cut-offs that were pre-defined (prior to study commencement), or selected based on the data (exploratory testing using the AUC/ROC). Studies utilising the AUC reported the optimal cut-off (where sensitivity and specificity were optimised), and/or the cut-offs that produced maximum sensitivity or maximum specificity. Other included studies reported a range of cut-offs where the reasoning for selection was unclear (arbitrary selection).

Due to the extensive range of thresholds reported by the included studies to identify proteinuria ≥300mg/24hours, the committee decided to review a graphical representation/overview (appendix M) of sensitivity and specificity for all thresholds available from the evidence, and in particular a PCR threshold of 30 mg/mmol (ratio 0.30) as it is the most commonly used in clinical practice (CG107 NICE guideline 2010), before focussing on other thresholds of interest (based on the graphical representation).

Benefits and harms

The main priority in testing for significant proteinuria is to ensure that women who have/may have pre-eclampsia are identified and offered appropriate follow up and monitoring. The gold standard for assessment/diagnosis of significant proteinuria is currently by 24 hour urine collection and analysis. This can cause delays in commencement of treatment, and the process itself can be awkward and cumbersome. Furthermore, the committee noted that, although this is regarded as the “gold standard”, the results still may be misleading. Samples may be incomplete, leading to an under-estimation of the quantity of protein. The quantity of protein excreted may also fluctuate slightly from day to day, therefore an individual woman may have a ”positive” result on one day, and a “negative” result on the next. Studies have also previously identified a lack of repeatability in laboratory based testing of proteinuria – the specific assay used to identify protein varies between individual laboratories, and may lead to an under/over-estimation of the degree of proteinuria. The committee discussed the reliability of this “gold standard” in itself and agreed that, though it was not perfectly reliable, as it stands it is the only appropriate reference standard for significant proteinuria (to compare to spot PCR and ACR).

From the woman’s perspective, the committee discussed the negative connotations associated with being labelled as having pre-eclampsia, often based on dipstick screening alone, before the results of a 24 hour urine collection were available. The committee discussed common situations, where women are hospitalised for suspected pre-eclampsia and undergo unnecessary further testing and monitoring, when ultimately significant proteinuria is never identified. The anxiety caused by such admissions, the disruption to the woman and her family, and the health economic issues associated with lengthy admission were discussed. There was a strong feeling that a quicker, easier, simpler, and accurate test for significant proteinuria in pregnancy should be favoured.

The sensitivity of both ACR and PCR tests at the thresholds recommended was high, giving confidence to women and health care professionals that those with a negative test do not have significant proteinuria. Therefore it was considered safe and appropriate to recommend the use of these tests in preference to a 24 hour urine collection. The committee noted that ACR and PCR may not be sufficient in pregnant women with additional comorbidities (such as renal disease in pregnancy). Therefore a 24 hour urine collection may still be appropriate and useful in a specialist setting.

The evidence presented showed that, by excluding the first morning urine void, diagnostic accuracy appeared to improve (both sensitivity and specificity). Evidence for this was only available for PCR analysis at a threshold of 30 mg/mmol, but the committee considered it was probably of relevance to other thresholds for PCR, and for ACR. The committee could only speculate on the reasons for the first morning urine void decreasing diagnostic accuracy. Possible factors could be the effects of posture overnight on kidney function, the concentration of the first urine void in the morning, and increased proteinuria associated with exercise. The committee therefore concluded it would be wise to recommend not using the first morning urine void, to maximise the diagnostic accuracy for both PCR and ACR.

The committee discussed the widespread use of urine dipstick analysis in both primary and secondary care settings. As per the previous version of this guideline, the committee agreed that automated dipstick analysis should be used as a screening test to establish whether a woman requires further testing using PCR or ACR, but it should not be used for a definitive diagnosis. The committee agreed that the use of visual analysis of a dipstick test was highly subjective, therefore should be minimised and halted where possible, to be replaced by automated dipstick analysis, at least in secondary care (for example, it would not be practicable to expect all community midwives to carry an automated reader with them). This should ensure that women who need further assessment of proteinuria, and those in whom proteinuria is not present, can be safely identified and followed up as appropriate.

The evidence for diagnostic accuracy for PCR clearly showed sensitivity as very high at lower thresholds - at such thresholds the false negative rate is very low (a negative result can be taken with high confidence), whereas specificity was very low at the lowest thresholds (very low confidence in a positive result). As the threshold increased, sensitivity began to drop, and specificity rose. The majority of the evidence for PCR was at the threshold of 30mg/mmol, which is already commonly used in clinical practice for the identification of significant proteinuria. At this threshold, meta-analysis of 10 studies (including over 3000 women) confirmed high sensitivity and high specificity, with comparatively narrow confidence intervals, therefore the committee supported the use of this threshold.

In discussing the evidence for ACR use in the identification of significant proteinuria, the committee discussed the reasoning and scientific rationale behind the use of albumin compared to total protein (as in PCR). The scientific rationale suggests that, as albumin is a small molecule, it can pass from the kidneys into the urine sooner than other proteins. Therefore albumin may appear in the urine and be detected by an ACR test in the early stages of pre-eclampsia, before proteinuria or clinical symptoms and signs of pre-eclampsia may be present. Detecting these low levels of albuminuria may be useful in early detection of proteinuria, to monitor women for the development of pre-eclampsia.

The evidence for ACR was not as clear as with PCR, due to the limited number of studies, with small sample sizes, that could be included within the review. Sensitivity was noted to be high across all studies, at every threshold. In assessing the available evidence, both sensitivity and specificity appeared to be maximised at a threshold of 8.0 mg/mmol. However, there were no data for thresholds between 3.5 mg/mmol and 8.0 mg/mmol. The single study which reported data at a threshold of 8.0 mg/mmol included only 150 women, and showed very wide confidence intervals for sensitivity. In addition to the evidence presented within the review, the committee were aware of, and discussed, additional data reported in a recent, large, UK-based study (Waugh 2017). This study assessed the

identification of proteinuria (with a reference standard of 24 hour urinary protein ≥300mg), and also the prediction of severe pre-eclampsia (with either the NICE definition of severe pre-eclampsia, or a clinician diagnosis of severe pre-eclampsia as the reference standard). For the purposes of this review, only the data relating to identification of proteinuria were relevant to the protocol.

The committee noted that Waugh 2017 presented additional data regarding the prediction of severe pre-eclampsia (as defined by NICE), which included further analyses of different ACR thresholds. In this analysis, it was noted that an ACR of 8.0 mg/mmol had comparable performance to that of a PCR of 30 mg/mmol. The ACR threshold of 8.0 mg/mmol was also used in a health economic model which was conducted as part of the Waugh study - which considered a clinical diagnosis of severe pre-eclampsia - and supported this ACR threshold as the most suitable and cost effective assessment.

Based on this additional information, and the limited evidence at 8.0 mg/mmol within this review, the committee supported the use of a threshold of 8mg/mmol for ACR when using this in the diagnosis of pre-eclampsia. The committee were aware that this threshold is different to that used for detection of microalbuminura in the non-pregnant population. However, they agreed that, on the basis of the evidence reviewed, it was appropriate to use a threshold of 8 mg/mmol for pregnant women.

Some ACR tests are designed as point-of-care or bedside assessments, and may be useful due to speed of obtaining the results. However, the data presented to the committee and used to aid decision making was based on ACR analysis performed within laboratories, and not at point-of-care. Consequently, the committee could not make a recommendation to use point-of-care ACR tests, and the recommendations regarding ACR results are based upon the diagnostic accuracy of laboratory tested spot/random urine samples. The committee discussed the potential for ACR point-of-care tests in the future, with improved technology allowing accurate and efficient testing to be undertaken, with results in minutes instead of the hours normally required for laboratory testing.

The difference in diagnostic accuracy for the identification of significant proteinuria was marginal between the two tests (PCR and ACR), therefore the committee did not recommend one test over the other. Local availability of the two tests could be used to determine which method is utilised. They noted that ACR testing was found to be more cost effective in the study by Waugh 2017, but again this was for the prediction of severe (clinician diagnosed) pre-eclampsia, rather than identification of significant proteinuria. The committee agreed that there was no benefit to performing both tests, as it provides no additional information.

The committee discussed when re-testing of ACR or PCR should be performed, if appropriate. No evidence addressing this issue was assessed. The committee noted that there is wide variation in the time taken for PCR and ACR results to be reported, and that this may impact on when a result should be repeated. Some laboratories are able to report a result within hours, while others take several days. It is unclear whether a false positive PCR or ACR result may resolve rapidly (over the course of the day), or whether it would be better to wait for several days before re-testing. Therefore this was left to the discretion of the health care professional, in discussion with the woman, taking into account other features of the pregnancy, clinical signs and symptoms of pre-eclampsia, and the local availability of testing, and the committee recommended that a re-testing schedule is developed according to the laboratory time available at local/regional level.

The committee noted that, whilst the evidence included in this review relates to the identification of proteinuria, a sequelae to that is often the diagnosis of pre-eclampsia. Typically, the urine may be checked because of an episode of hypertension. Therefore the identification of proteinuria in that urine sample would consequently lead to a firm diagnosis of pre-eclampsia being made, and a woman being offered intensive monitoring, follow up, and possible admission to hospital. The committee were aware that proteinuria is occasionally found to resolve on a subsequent urine sample (particularly when the initial

sample showed a relatively low level of protein). Therefore they recommended consideration of repeating the PCR or ACR measurement in the absence of any other clinical symptoms or signs of pre-eclampsia. Clearly, if other defining features of pre-eclampsia were present, then the proteinuria result may need no confirmation.

The committee reiterated throughout the discussion that the results of either ACR or PCR in the assessment of proteinuria should be interpreted alongside the presence of hypertension and the other clinical signs and symptoms of pre-eclampsia. As emphasised at the start of this evidence report, and in keeping with international guidelines, the absence of proteinuria does not exclude the possibility of pre-eclampsia. Some women may develop other clinical features of the condition before developing significant proteinuria. Furthermore, although the sensitivity of ACR and PCR tests is high, false negative results may still occur. Therefore clinicians and women need to be vigilant to the other symptoms and signs of the disease, and not rely on the presence or absence of significant proteinuria alone as a defining feature.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

Use of spot urine tests for PCR or ACR should reduce the delay in identifying significant proteinuria, as compared with using a 24 hour urine test. This should reduce unnecessary hospital admissions for women in whom proteinuria can be confidently excluded. Furthermore, it will allow targeted follow up for women who are found to have a positive result.

Women who have a positive result for significant proteinuria are currently offered intensive follow up and monitoring, due to the suspicion/diagnosis of pre-eclampsia. Repeating the PCR/ACR tests for those with marginally elevated results is likely to increase the number of tests requested. However, this should also improve the diagnostic accuracy, by detecting those women in whom the first result was falsely positive. This will allow a step-down in follow up and monitoring for these women, reducing unnecessary resource use.

Other factors the committee took into account

The committee reviewed a graphical representation of the data regarding sensitivity and specificity of the PCR and ACR tests at different thresholds (Appendix M). This highlighted the high sensitivity and specificity of ACR at a threshold of 8mg/mmol, although the wide confidence interval for sensitivity was noted. Similarly, the committee noted the high sensitivity and specificity at a PCR threshold of 30mg/mmol, with comparatively narrow confidence intervals around the point estimate from the meta-analysis.

As discussed above, the committee were aware of the large diagnostic accuracy study (Waugh 2017) that was commissioned as a result of the previous guideline. Only the data which considered identification of significant proteinuria (reference standard ≥300mg in 24 hours) were directly relevant to this systematic review. However, the committee were aware of, and discussed, the other findings of the study – including reference standards of a diagnosis of severe pre-eclampsia (either as defined in this guideline, or a clinician diagnosis). The committee agreed that these were also important and relevant outcomes, which should be taken into account when appraising the evidence.

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Appendices

Appendix A – Review protocol

Table 3: Review protocol

Field (based on PRISMA-P)	Content
Key area in the scope	Assessment of proteinuria in hypertensive disorders of pregnancy
Draft review question from the previous guideline (to be deleted in the final version)	(no question in the existing guideline)
Actual review question	How effective are spot protein/creatinine ratio or albumin/creatinine ratio measurements as compared with a 24 hour urine collection for the identification of proteinuria in women with hypertensive disorders of pregnancy?
Type of review question	Diagnostic accuracy question
Objective of the review	To update the recommendations in the previous guideline (CG107) for the measurement of proteinuria – surveillance has indicated that the DAPPA study may influence the method by which proteinuria should be identified (recs 1.3.1.3 and 1.3.1.4). 24 hour collection of urine is currently viewed as the reference standard to diagnose proteinuria. However, it is inconvenient for women, costly and time consuming to complete these collections. This can resulting in a delay in diagnosis or missed diagnosis (due to incomplete samples). Identification of a simpler, quicker, yet effective, method to demonstrate significant proteinuria has the potential to improve this.
Eligibility criteria – population/disease/condition/issue/domain	Pregnant women with hypertension. This population includes women with: • chronic hypertension • gestational hypertension • suspected pre-eclampsia
Eligibility criteria – Index test(s)	Spot albumin:creatinine ratio (ACR) Spot protein:creatinine ratio (PCR)

Field (based on PRISMA-P)	Content
Eligibility criteria – reference (gold) standard	Urinary protein excretion of ≥300mg in 24 hours
Outcomes and prioritisation	Critical outcomes • Sensitivity • Negative likelihood ratio Important outcomes • Area under the curve (AUC) • Positive likelihood ratio • Specificity
Eligibility criteria – study design	Only published full text papers in English language Cross-sectional diagnostic accuracy studies
Exclusion criteria	
Proposed stratified, sensitivity/sub-group analysis, or meta-regression	If different diagnostic thresholds are used for the reference standard (e.g. 300mg protein in 24 hours and 500mg protein in 24 hours) then these will be analysed separately.
Selection process – duplicate screening/selection/analysis	Duplicate screening/selection/analysis will not be undertaken for this review as this question was not prioritised for it. Included and excluded studies will be cross checked with the committee and with published systematic reviews when available.
Data management (software)	Meta-analyses will be performed where appropriate. A bivariate random effects model will be used, for example with the metandi package for STATA. 'GRADE' will be used to assess the quality of evidence for each outcome. STAR will be used bibliographies/citations, text mining, and study sifting, data extraction and quality assessment/critical appraisal. Microsoft Word will be used for data extraction and quality assessment/critical appraisal

Field (based on PRISMA-P)	Content
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase. Limits (e.g. date, study design): Study design limited to Systematic Reviews, RCTs and Comparative Cohort Studies. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies.
Identify if an update	This is an update. Studies meeting the current protocol criteria and previously included in the 2010 guideline (CG107) will be included in this update.
Author contacts	Developer: National Guideline Alliance Systematic reviewer: Louise Geneen Health economist: Matthew Prettyjohns Information specialist: Tim Reeves
Highlight if amendment to previous protocol	Although this topic was included in the existing guideline, no specific review question or protocol was developed, as the topic was addressed as a sub-question of other reviews.
Search strategy – for one database	For details please see appendix B of the full guideline
Data collection process – forms/duplicate	Studies included in the previous guideline (CG107) that meet the inclusion criteria of this protocol will be re-extracted in a standardised evidence table and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For clinical evidence tables (appendix D), the following data items will be collected: full reference, study ID, type of study, objective country/ies where the study was carried out, inclusion criteria, exclusion criteria, methods, results and limitations.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: QUADAS-II

Field (based on PRISMA-P)	Content
	For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/. Studies included in the previous guideline (CG107) that meet the inclusion criteria of this protocol will be assessed with the above mentioned checklists (as appropriate) and outcomes will be evaluated using GRADE.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analyses will be performed where appropriate. A bivariate random effects model will be used, for example with the metandi package for STATA. **Minimum important differences:** The cut-offs for diagnostic accuracy measures: **Sensitivity and specificity:** ≥ 90% very useful test < 75% not a useful test Double sifting, data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction will not be performed. How the evidence included in the previous guideline will be incorporated with the new evidence

Field (based on PRISMA-P)	Content
	Studies meeting the current protocol criteria and previously included in the 2010 guideline (CG107) will be included in this update. The methods for quantitative analysis –combining studies and exploring (in)consistency- will be the same as for the new evidence (see above).
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee [add link to history page of the guideline] developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered to PROSPERO

Appendix B – Literature search strategies

Review question search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 02/05/18

#	Searches
1	HYPERTENSION, PREGNANCY-INDUCED/
2	PREGNANCY/ and HYPERTENSION/
3	PRE-ECLAMPSIA/
4	HELLP SYNDROME/
5	((pregnan$ or gestation$) adj5 hypertensi$).ti.
6	preeclamp$.ti,ab.
7	pre eclamp$.ti,ab.
8	HELLP.ti,ab.
9	tox?emi$.ti,ab.
10	(positive$ adj5 (dipstick? or dip-stick?)).ti,ab.
11	((1+ or >=1+) adj5 (dipstick? or dip-stick?)).ti,ab.
12	or/1-9
13	or/1-11
14	(URINE/ or URINE SPECIMEN COLLECTION/) and TIME FACTORS/
15	(("24" or twenty four) adj3 (hour? or hr? or h?) adj5 urin$).ti,ab.
16	(24h$ adj5 urin$).ti,ab.
17	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) adj5 ("24" or twenty four) adj3 (hour? or hr? or h?)).ti,ab.
18	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) adj5 24h$).ti,ab.
19	or/14-18
20	PROTEINS/ and CREATININE/
21	ALBUMINS/ and CREATININE/
22	((spot$ or ratio$) adj5 (protein$ or creatinine or albumin$)).ti,ab.
23	(P?CR or SPCR or A?CR or SACR).ti,ab.
24	(spot$ adj3 urin$).ti,ab.
25	or/20-24
26	PROTEINURIA/
27	proteinuria?.ti,ab.
28	or/26-27
29	Positive likelihood ratio?.ti,ab.
30	LR+.ti,ab.
31	Negative likelihood ratio?.ti,ab.
32	LR-.ti,ab.
33	AREA UNDER CURVE/
34	(area? under adj2 curve?).ti,ab.
35	AUC?.ti,ab.
36	"SENSITIVITY AND SPECIFICITY"/
37	(sensitiv$ adj10 specific$).ti,ab.
38	or/29-37
39	*PROTEINURIA/di [Diagnosis]
40	*URINALYSIS/mt [Methods]
41	13 and 19 and 25
42	12 and (19 or 25) and 28 and 38
43	13 and 19 and 39
44	13 and 25 and 39
45	12 and 40
46	or/41-45
47	limit 46 to english language
48	LETTER/
49	EDITORIAL/
50	NEWS/
51	exp HISTORICAL ARTICLE/

#	Searches
52	ANECDOTES AS TOPIC/
53	COMMENT/
54	CASE REPORT/
55	(letter or comment*).ti.
56	or/48-55
57	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
58	56 not 57
59	ANIMALS/ not HUMANS/
60	exp ANIMALS, LABORATORY/
61	exp ANIMAL EXPERIMENTATION/
62	exp MODELS, ANIMAL/
63	exp RODENTIA/
64	(rat or rats or mouse or mice).ti.
65	or/58-64
66	47 not 65

Databases: Embase; and Embase Classic

Date of last search: 02/05/18

#	Searches
1	MATERNAL HYPERTENSION/
2	PREGNANCY/ and HYPERTENSION/
3	PREECLAMPSIA/
4	HELLP SYNDROME/
5	((pregnan$ or gestation$) adj5 hypertensi$).ti.
6	preeclamp$.ti,ab.
7	pre eclamp$.ti,ab.
8	HELLP.ti,ab.
9	tox?emi$.ti,ab.
10	(positive$ adj5 (dipstick? or dip-stick?)).ti,ab.
11	((1+ or >=1+) adj5 (dipstick? or dip-stick?)).ti,ab.
12	or/1-9
13	or/1-11
14	(URINE/ or URINE SAMPLING/) and TIME FACTOR/
15	(("24" or twenty four) adj3 (hour? or hr? or h?) adj5 urin$).ti,ab.
16	(24h$ adj5 urin$).ti,ab.
17	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) adj5 ("24" or twenty four) adj3 (hour? or hr? or h?)).ti,ab.
18	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) adj5 24h$).ti,ab.
19	or/14-18
20	PROTEIN/ and CREATININE/
21	ALBUMIN/ and CREATININE/
22	((spot$ or ratio$) adj5 (protein$ or creatinine or albumin$)).ti,ab.
23	(P?CR or SPCR or A?CR or SACR).ti,ab.
24	(spot$ adj3 urin$).ti,ab.
25	or/20-24
26	PROTEINURIA/
27	proteinuria?.ti,ab.
28	or/26-27
29	Positive likelihood ratio?.ti,ab.
30	LR+.ti,ab.
31	Negative likelihood ratio?.ti,ab.
32	LR-.ti,ab.
33	AREA UNDER THE CURVE/
34	(area? under adj2 curve?).ti,ab.
35	AUC?.ti,ab.
36	"SENSITIVITY AND SPECIFICITY"/
37	(sensitiv$ adj10 specific$).ti,ab.
38	or/29-37
39	*PROTEINURIA/di [Diagnosis]
40	13 and 19 and 25

#	Searches
41	12 and (19 or 25) and 28 and 38
42	13 and 19 and 39
43	13 and 25 and 39
44	or/40-43
45	limit 44 to english language
46	letter.pt. or LETTER/
47	note.pt.
48	editorial.pt.
49	CASE REPORT/ or CASE STUDY/
50	(letter or comment*).ti.
51	or/46-50
52	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
53	51 not 52
54	ANIMAL/ not HUMAN/
55	NONHUMAN/
56	exp ANIMAL EXPERIMENT/
57	exp EXPERIMENTAL ANIMAL/
58	ANIMAL MODEL/
59	exp RODENT/
60	(rat or rats or mouse or mice).ti.
61	or/53-60
62	45 not 61

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

Date of last search: 02/05/18

#	Searches
1	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] this term only
2	MeSH descriptor: [PREGNANCY] this term only
3	MeSH descriptor: [HYPERTENSION] this term only
4	#2 and #3
5	MeSH descriptor: [PRE-ECLAMPSIA] this term only
6	MeSH descriptor: [HELLP SYNDROME] this term only
7	((pregnan* or gestation*) near/5 hypertensi*):ti
8	preeclamp*:ti,ab
9	pre eclamp*:ti,ab
10	HELLP:ti,ab
11	tox?emi*:ti,ab
12	(positive* near/5 (dipstick? or dip-stick?)):ti,ab
13	#1 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
14	#1 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
15	MeSH descriptor: [URINE] this term only
16	MeSH descriptor: [URINE SPECIMEN COLLECTION] this term only
17	#15 or #16
18	MeSH descriptor: [TIME FACTORS] this term only
19	#17 and #18
20	(("24" or twenty four) near/3 (hour? or hr? or h?) near/5 urin*):ti,ab
21	(24h* near/5 urin*):ti,ab
22	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) near/5 ("24" or twenty four) near/3 (hour? or hr? or h?)):ti,ab
23	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) near/5 24h*):ti,ab
24	#19 or #20 or #21 or #22 or #23
25	MeSH descriptor: [PROTEINS] this term only
26	MeSH descriptor: [CREATININE] this term only
27	#25 and #26
28	MeSH descriptor: [ALBUMINS] this term only
29	#26 and #28
30	((spot* or ratio*) near/5 (protein* or creatinine or albumin*)):ti,ab

#	Searches
31	(P?CR or SPCR or A?CR or SACR):ti,ab
32	(spot* near/3 urin*):ti,ab
33	#27 or #29 or #30 or #31 or #32
34	MeSH descriptor: [PROTEINURIA] this term only
35	Proteinuria*:ti,ab
36	#34 or #35
37	Positive likelihood ratio?:ti,ab
38	Negative likelihood ratio?:ti,ab
39	MeSH descriptor: [AREA UNDER CURVE] this term only
40	(area? under near/2 curve?):ti,ab
41	AUC?:ti,ab
42	MeSH descriptor: [SENSITIVITY AND SPECIFICITY] this term only
43	(sensitiv* near/10 specific*):ti,ab
44	#37 or #38 or #39 or #40 or #41 or #42 or #43
45	MeSH descriptor: [PROTEINURIA] this term only and with qualifier(s): [Diagnosis - DI]
46	MeSH descriptor: [URINALYSIS] this term only and with qualifier(s): [Methods - MT]
47	#14 and #24 and #33
48	#13 and (#24 or #33) and #36 and #44
49	#14 and #24 and #45
50	#14 and #33 and #45
51	#13 and #46
52	#47 or #48 or #49 or #50 or #51

Health economics search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 02/05/18

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	HYPERTENSION, PREGNANCY-INDUCED/
23	PREGNANCY/ and HYPERTENSION/
24	PRE-ECLAMPSIA/
25	HELLP SYNDROME/
26	((pregnan$ or gestation$) adj5 hypertensi$).ti.
27	preeclamp$.ti,ab.
28	pre eclamp$.ti,ab.
29	HELLP.ti,ab.
30	tox?emi$.ti,ab.

#	Searches
31	(positive$ adj5 (dipstick? or dip-stick?)).ti,ab.
32	((1+ or >=1+) adj5 (dipstick? or dip-stick?)).ti,ab.
33	or/22-30
34	or/22-32
35	(URINE/ or URINE SPECIMEN COLLECTION/) and TIME FACTORS/
36	(("24" or twenty four) adj3 (hour? or hr? or h?) adj5 urin$).ti,ab.
37	(24h$ adj5 urin$).ti,ab.
38	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) adj5 ("24" or twenty four) adj3 (hour? or hr? or h?)).ti,ab.
39	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) adj5 24h$).ti,ab.
40	or/35-39
41	PROTEINS/ and CREATININE/
42	ALBUMINS/ and CREATININE/
43	((spot$ or ratio$) adj5 (protein$ or creatinine or albumin$)).ti,ab.
44	(P?CR or SPCR or A?CR or SACR).ti,ab.
45	(spot$ adj3 urin$).ti,ab.
46	or/41-45
47	PROTEINURIA/
48	proteinuria?.ti,ab.
49	or/47-48
50	Positive likelihood ratio?.ti,ab.
51	LR+.ti,ab.
52	Negative likelihood ratio?.ti,ab.
53	LR-.ti,ab.
54	AREA UNDER CURVE/
55	(area? under adj2 curve?).ti,ab.
56	AUC?.ti,ab.
57	"SENSITIVITY AND SPECIFICITY"/
58	(sensitiv$ adj10 specific$).ti,ab.
59	or/50-58
60	*PROTEINURIA/di [Diagnosis]
61	*URINALYSIS/mt [Methods]
62	34 and 40 and 46
63	33 and (40 or 46) and 49 and 59
64	34 and 40 and 60
65	34 and 46 and 60
66	33 and 61
67	or/62-66
68	limit 67 to english language
69	LETTER/
70	EDITORIAL/
71	NEWS/
72	exp HISTORICAL ARTICLE/
73	ANECDOTES AS TOPIC/
74	COMMENT/
75	CASE REPORT/
76	(letter or comment*).ti.
77	or/69-76
78	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
79	77 not 78
80	ANIMALS/ not HUMANS/
81	exp ANIMALS, LABORATORY/
82	exp ANIMAL EXPERIMENTATION/
83	exp MODELS, ANIMAL/
84	exp RODENTIA/
85	(rat or rats or mouse or mice).ti.
86	or/79-85
87	68 not 86
88	21 and 87

Databases: Embase; and Embase Classic

Date of last search: 02/05/18

#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16
18	MATERNAL HYPERTENSION/
19	PREGNANCY/ and HYPERTENSION/
20	PREECLAMPSIA/
21	HELLP SYNDROME/
22	((pregnan$ or gestation$) adj5 hypertensi$).ti.
23	preeclamp$.ti,ab.
24	pre eclamp$.ti,ab.
25	HELLP.ti,ab.
26	tox?emi$.ti,ab.
27	(positive$ adj5 (dipstick? or dip-stick?)).ti,ab.
28	((1+ or >=1+) adj5 (dipstick? or dip-stick?)).ti,ab.
29	or/18-26
30	or/18-28
31	(URINE/ or URINE SAMPLING/) and TIME FACTOR/
32	(("24" or twenty four) adj3 (hour? or hr? or h?) adj5 urin$).ti,ab.
33	(24h$ adj5 urin$).ti,ab.
34	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) adj5 ("24" or twenty four) adj3 (hour? or hr? or h?)).ti,ab.
35	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) adj5 24h$).ti,ab.
36	or/31-35
37	PROTEIN/ and CREATININE/
38	ALBUMIN/ and CREATININE/
39	((spot$ or ratio$) adj5 (protein$ or creatinine or albumin$)).ti,ab.
40	(P?CR or SPCR or A?CR or SACR).ti,ab.
41	(spot$ adj3 urin$).ti,ab.
42	or/37-41
43	PROTEINURIA/
44	proteinuria?.ti,ab.
45	or/43-44
46	Positive likelihood ratio?.ti,ab.
47	LR+.ti,ab.
48	Negative likelihood ratio?.ti,ab.
49	LR-.ti,ab.
50	AREA UNDER THE CURVE/
51	(area? under adj2 curve?).ti,ab.
52	AUC?.ti,ab.
53	"SENSITIVITY AND SPECIFICITY"/
54	(sensitiv$ adj10 specific$).ti,ab.
55	or/46-54
56	*PROTEINURIA/di [Diagnosis]
57	30 and 36 and 42
58	29 and (36 or 42) and 45 and 55
59	30 and 36 and 56
60	30 and 42 and 56

#	Searches
61	or/57-60
62	limit 61 to english language
63	letter.pt. or LETTER/
64	note.pt.
65	editorial.pt.
66	CASE REPORT/ or CASE STUDY/
67	(letter or comment*).ti.
68	or/63-67
69	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
70	68 not 69
71	ANIMAL/ not HUMAN/
72	NONHUMAN/
73	exp ANIMAL EXPERIMENT/
74	exp EXPERIMENTAL ANIMAL/
75	ANIMAL MODEL/
76	exp RODENT/
77	(rat or rats or mouse or mice).ti.
78	or/70-77
79	62 not 78
80	17 and 79

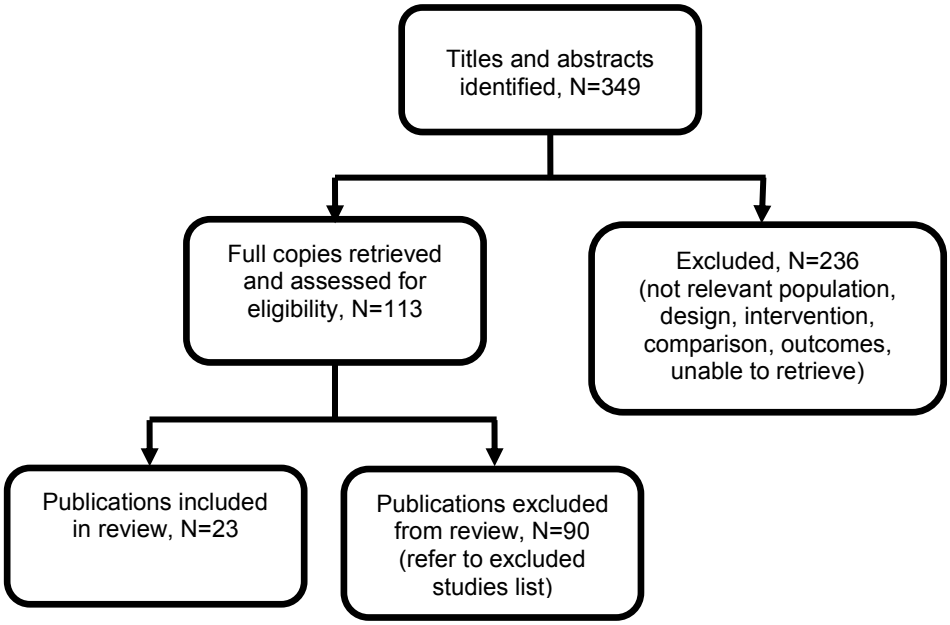
Databases: Cochrane Central Register of Controlled Trials; Health Technology Assessment; and NHS Economic Evaluation Database

Date of last search: 02/05/18

#	Searches
1	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] this term only
2	MeSH descriptor: [PREGNANCY] this term only
3	MeSH descriptor: [HYPERTENSION] this term only
4	#2 and #3
5	MeSH descriptor: [PRE-ECLAMPSIA] this term only
6	MeSH descriptor: [HELLP SYNDROME] this term only
7	((pregnan* or gestation*) near/5 hypertensi*):ti
8	preeclamp*:ti,ab
9	pre eclamp*:ti,ab
10	HELLP:ti,ab
11	tox?emi*:ti,ab
12	(positive* near/5 (dipstick? or dip-stick?)):ti,ab
13	#1 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
14	#1 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
15	MeSH descriptor: [URINE] this term only
16	MeSH descriptor: [URINE SPECIMEN COLLECTION] this term only
17	#15 or #16
18	MeSH descriptor: [TIME FACTORS] this term only
19	#17 and #18
20	(("24" or twenty four) near/3 (hour? or hr? or h?) near/5 urin*):ti,ab
21	(24h* near/5 urin*):ti,ab
22	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) near/5 ("24" or twenty four) near/3 (hour? or hr? or h?)):ti,ab
23	((300 mg or >=300 mg or 300mg or >=300mg or 500 mg or >=500 mg or 500mg or >=500mg) near/5 24h*):ti,ab
24	#19 or #20 or #21 or #22 or #23
25	MeSH descriptor: [PROTEINS] this term only
26	MeSH descriptor: [CREATININE] this term only
27	#25 and #26
28	MeSH descriptor: [ALBUMINS] this term only
29	#26 and #28
30	((spot* or ratio*) near/5 (protein* or creatinine or albumin*)):ti,ab
31	(P?CR or SPCR or A?CR or SACR):ti,ab
32	(spot* near/3 urin*):ti,ab
33	#27 or #29 or #30 or #31 or #32
34	MeSH descriptor: [PROTEINURIA] this term only

#	Searches
35	Proteinuria*:ti,ab
36	#34 or #35
37	Positive likelihood ratio?:ti,ab
38	Negative likelihood ratio?:ti,ab
39	MeSH descriptor: [AREA UNDER CURVE] this term only
40	(area? under near/2 curve?):ti,ab
41	AUC?:ti,ab
42	MeSH descriptor: [SENSITIVITY AND SPECIFICITY] this term only
43	(sensitiv* near/10 specific*):ti,ab
44	#37 or #38 or #39 or #40 or #41 or #42 or #43
45	MeSH descriptor: [PROTEINURIA] this term only and with qualifier(s): [Diagnosis - DI]
46	MeSH descriptor: [URINALYSIS] this term only and with qualifier(s): [Methods - MT]
47	#14 and #24 and #33
48	#13 and (#24 or #33) and #36 and #44
49	#14 and #24 and #45
50	#14 and #33 and #45
51	#13 and #46
52	#47 or #48 or #49 or #50 or #51

Appendix C – Clinical evidence study selection



Appendix D – Clinical evidence tables

Table 4: Clinical evidence tables

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Al, R. A., Baykal, C., Karacay, O., Geyik, P. O., Altun, S., Dolen, I., Random urine protein-creatinine ratio to predict proteinuria in new-onset mild hypertension in late pregnancy, Obstetrics & Gynecology, 104, 367-71, 2004

Ref Id

658834

Country/ies where the study was carried out

Turkey

Study type

Retrospective cohort study

Aim of the study
to assess diagnostic accuracy of random urine protein:creatinine ratio for prediction of significant proteinuria in patients with new onset mild hypertension in late pregnancy</td>
<td>Sample size
n=185

Characteristics
Age, median, years (range): 30 (17-44)
Gestation, mean, weeks (SD): 32 (4)
BP not reported

Inclusion Criteria
pregnant women with new onset mild hypertension (≥140/90mmHg) in late pregnancy

Exclusion Criteria
severe hypertension (>160/110mmHg measured twice at least 6 hrs apart), elevated liver enzymes, low platelet count syndrome, thrombocytopenia, eclampsia, IUGR,</td>
<td>Tests
<u>Index test:</u> random urine protein:creatinine ratio (trichloroacetic acid reaction test)
<u>Reference standard:</u> ≥ 300mg urinary protein excretion/24 hours</td>
<td>Methods
24-hour urine collections were started between 9am-12noon
All random samples were collected in the morning before the start of the 24-hour urine collection
Urine protein concentration was measured by trichloroacetic acid reaction (coefficient of variation 9%). The urinary creatinine test was performed with the Beckman Synchron LX Delta System (Beckman Instruments, Richmond, CA), which uses the Jaffe rate method.</td>
<td>Results
AUC: 0.86 (0.80 to 0.93)
<u>Cut off 0.19</u> Sensitivity 85% (70 to 94)Specificity 73% (65 to 80)
<table>
<tr><th></th><th>Reference test +</th><th>Reference test -</th><th>Total</th></tr>
<tr><td>Index test +</td><td>33</td><td>39</td><td>72</td></tr>
<tr><td>Index test -</td><td>6</td><td>107</td><td>113</td></tr>
<tr><td>Total</td><td>39</td><td>146</td><td>185</td></tr>
</table>
Alternative cut points
<u>Cut off 0.13</u> Sensitivity 90% (76 to 97)Specificity 65% (57 to 73)
<table>
<tr><th></th><th>Reference test +</th><th>Reference test -</th><th>Total</th></tr>
<tr><td>Index test +</td><td>35</td><td>51</td><td></td></tr>
<tr><td>Index test -</td><td>4</td><td>95</td><td></td></tr>
<tr><td>Total</td><td>39</td><td>146</td><td>185</td></tr>
</table>
<u>Cut off 0.18</u> Sensitivity 85% (70 to 94)Specificity 71% (63 to 78)</td>
<td>Limitations Risk of bias assessed using QUADAS-II
<u>DOMAIN 1: PATIENT SELECTION</u>
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? yes
2. Was a case-control design avoided? yes
3. Did the study avoid inappropriate</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Study dates
January 2002 - June 2003

Source of funding
Not reported</td>
<td>chronic hypertension, pre-existing renal disease, co-existing urinary tract infection, inadequate specimen collection</td>
<td></td>
<td></td>
<td>
<table>
<tr><td></td><td>Reference test +</td><td>Reference test -</td><td>Total</td></tr>
<tr><td>Index test +</td><td>33</td><td>42</td><td></td></tr>
<tr><td>Index test -</td><td>6</td><td>104</td><td></td></tr>
<tr><td>Total</td><td>39</td><td>146</td><td>185</td></tr>
</table>
Cut off 0.20 Sensitivity 80% (64 to 91)Specificity 74% (66 to 81)
<table>
<tr><td></td><td>Reference test +</td><td>Reference test -</td><td>Total</td></tr>
<tr><td>Index test +</td><td>31</td><td>38</td><td></td></tr>
<tr><td>Index test -</td><td>8</td><td>108</td><td></td></tr>
<tr><td>Total</td><td>39</td><td>146</td><td>185</td></tr>
</table>
Cut off 0.49 Sensitivity 74% (58 to 87)Specificity 84% (77 to 90)
<table>
<tr><td></td><td>Reference test +</td><td>Reference test -</td><td>Total</td></tr>
<tr><td>Index test +</td><td>29</td><td>23</td><td></td></tr>
<tr><td>Index test -</td><td>10</td><td>123</td><td></td></tr>
<tr><td>Total</td><td>39</td><td>146</td><td>185</td></tr>
</table>
</td>
<td>exclusions? yes

Could the selection of patients have introduced bias? RISK: LOW
B. CONCERNS REGARDING APPLICABILITY Is there concern that the included patients do not match the review question? CONCERN: LOW

<u>DOMAIN 2: INDEX TESTS</u>
A. RISK OF BIAS

1. Were the index test results interpreted</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? unclear **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition ? yes 2. Were the reference standard results interpreted without knowledge of the results of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					the index test? unc lear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. RISK OF BIAS 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? Yes 4. Were all patients included in the analysis? No – included

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					n=185/204; 91% (n=221 with new onset mild hypertension; 204 who had 24hr urine analysis) **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Amin, S. V., Illipilla, S., Hebbar, S., Rai, L., Kumar, P., Pai, M. V., Quantifying Proteinuria in Hypertensive Disorders of Pregnancy, International Journal of Hypertension, 2014, 941408, 2015 **Ref Id** 812372	**Sample size** n=102 (n=78 with proteinuria≥300mg/24hrs) **Characteristics** age: 27.4 ± 4.3 (20–41) years GA at delivery: 35.3 ± 3.3 (25–39) weeks	**Tests** Index test: random urine protein estimation (PCR) Reference test: 24 hour urine collection	**Methods** 24 hour urine collection: 24-hour urine protein estimation was carried out after admission. Patient was asked to discard the first void early morning sample.	**Results** cut-off values: 0.30, 0.45, 0.60, 0.75, 0.90 to predict proteinuria of >=300mg/day 0.30: Sens 89.7; Spec 54.2; LR+ 1.96; LR- 0.19; [TP 70; FP 11; FN 8; TN 13; back calculated by NGA] **0.45: 82.1; 87.5; 6.56; 0.21; AUC: 0.89 (0.83-0.95) [TP 64; FP 3; FN 14; TN 21; back calculated by NGA]** 0.60: 75.6; 87.5; 6.05; 0.28; [TP 59; FP 3; FN 19; TN 21; back calculated by NGA]	**Limitations** **Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecutive or

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out India **Study type** Prospective cohort study **Aim of the study** comparison of diagnostic utility of two tests: urine dipstick method and spot urine protein:creatinine ratio in diagnosis of significant proteinuria in patients with hypertensive disorder of pregnancy **Study dates** July 2009 - June 2011 **Source of funding** Manipal University institutional grant	**Inclusion Criteria** Hypertensive disorders of pregnancy, recruited after GA 20weeks (hypertension: DBP>90, and SBP>110; or increase in SBP by 30 and DBP by 15) **Exclusion Criteria** all cases of chronic renal disease, secondary hypertension due to immunological diseases such as lupus erythematosus, and overt diabetes mellitus. Patients who delivered due to urgent indications for termination of pregnancy (could not complete 24-hour collection)			0.75: 67.9; 100; 33.29; 0.32 [TP 53; FP 0; FN 25; TN 24; back calculated by NGA] 0.90: 61.5; 100; 30.15; 0.38 [TP 48; FP 0; FN 30; TN 24]; back calculated by NGA]	random sample of patients enrolled? unclear 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard likely to correctly classify the target condition ? yes 2. Were the referenc e standard results interpret ed without knowled ge of the results of the index test? unc lear **Could the reference standard, its conduct, or its interpretatio n have introduced bias? RISK:LOW** **B. CONCERNS REGARDIN**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					G APPLICABILITY Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard ? yes 2. Did all patients receive a

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					3. Did patients receive the same reference standard? yes 4. Were all patients included in the analysis? yes **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Bhatti, S., Cordina, M., Penna, L., Sherwood, R., Dew, T., Kametas, N. A., The effect of ethnicity on the performance of protein-	**Sample size** n=476 (all ethnicities) (n=106 with proteinuria≥300mg/24hrs; n=370 with <300)	**Tests** Index test: urine sample for PCR after completion of 24 hour collection Reference test: 24 hour urine collection	**Methods** Each patient provided a urine sample for the calculation of the PCR immediately after the completion of the 24-h urine collection. The urine samples	**Results** n=106 with proteinuria≥300mg/24hrs; n=370 with <300 **PCR cut-off: 30mg/mmol and "optimal" based on ROC curve**	**Limitations Risk of bias assessed using QUADAS-II**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
creatinine ratio in the prediction of significant proteinuria in pregnancies at risk of or with established hypertension: an implementation audit and cost implications, Acta Obstetricia et Gynecologica Scandinavica, 97, 598-607, 2018 **Ref Id** 838660 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** assess the performance of PCR to predict proteinuria of ≥300 mg in a 24-h concentration in an antenatal population and comparing its cost-efficiency in black and nonblack populations **Study dates** January 2011 - December 2012	**Characteristics** 204 women of white, 239 women of black and 33 women with other (mixed) ethnicity age: 33.7 SD 5.6 years GA at referral: 35.3 (IQR 30.3-37.7) weeks **Inclusion Criteria** attending an antenatal hypertension clinic during study period: women with an increased risk of hypertensive complications, such as chronic hypertension or a history of hypertension in a previous pregnancy, women with new onset hypertension during their pregnancy **Exclusion Criteria** None reported		for PCR were not early morning samples PCR: Urinary protein quantitation was determined by the pyrogallol red molybdate dye-binding assay with the Advia 2400 analyzer (Siemens Healthcare, Frimley, Surrey) and urinary creatinine was determined by the modified Jaffe's reaction	30 mg/mmol: Sens 64.7 (54.8-73.8); Spec 94.6 (91.8-96.7); **[TP 69; FP 20; FN 37; TN 350; back calculated by NGA]** **"optimal for entire cohort" 20.56 mg/mmol:** 87.6 (79.8-93.2); 83.0 (78.9-86.7); **[TP 93; FP 63; FN 13, TN 307; back calculated by NGA]**	**DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding No specific funding grant					**B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard? unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					2. If a threshold was used, was it pre-specified ? unclear **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					DOMAIN 3: REFERENCE STANDARD **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					its interpretation have introduced bias? RISK:LOW **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 5. Was there appropriate interval

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					between index tests and reference standard? yes 6. Did all patients receive a reference standard? yes 7. Did patients receive the same reference standard? Yes 8. Were all patients included in the analysis? yes **Could the patient flow have introduced bias? RISK: LOW**

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Durnwald, C., Mercer, B., A prospective comparison of total protein/creatinine ratio versus 24-hour urine protein in women with suspected preeclampsia, American Journal of Obstetrics & Gynecology, 189, 848-52, 2003

Ref Id

658885

Country/ies where the study was carried out

USA

Study type

Prospective cohort study

Aim of the study
to assess the value of protein/creatinine ratio in prediction of 24 hour urinary protein in women with suspected pre-eclampsia</td><td>Sample size
n=220

Characteristics
Age, mean, years: 26.1
Gestation, mean, weeks: 36.5
BP not reported

Inclusion Criteria
pregnant women ≥ 24 weeks gestation, undergoing evaluation for suspected pre-eclampsia (including ≥ 1 of the following: hypertension, oedema, new-onset proteinuria on dipstick)

Exclusion Criteria
chronic hypertension, diabetes mellitus, renal disease, pre-existing proteinuria (1+ dipstick on initial office visit)</td><td>Tests
<u>Index test:</u> random urine protein:creatinine ratio (biuret reaction test)
<u>Reference standard:</u> ≥ 300mg urinary protein excretion/24 hours</td><td>Methods
a random urine collection was collected for the calculation of the protein/creatinine ratio before the initiation of the 24-hour urine collection
Proteinuria on 24-hour urine collection was defined as ‘‘significant’’ (>=300 mg) or ‘‘severe’’ (>=5000 mg), and mild proteinuria was defined as 300 to 4999 mg. Urinary protein quantitation was determined by the biuret reaction, and urinary creatinine was determined by the modified Jaffe´ reaction (Roche Laboratories)</td><td>Results
AUC: 0.80
n.b. cut offs are given as mg/g. Approximated to mg/mmol by conversion factor of 0.1, although actual conversion factor 0.113 <u>Cut off ~0.15 (150mg/g)</u>Sensitivity 92.9%Specificity 32.7%
<table><tr><td></td><td>Reference test +</td><td>Reference test -</td><td>Total</td></tr><tr><td>Index test +</td><td>156</td><td>35</td><td>191</td></tr><tr><td>Index test -</td><td>12</td><td>17</td><td>29</td></tr><tr><td>Total</td><td>168</td><td>52</td><td>220</td></tr></table><u>Cut off ~0.2 (200mg/g)</u>
Sensitivity 90.5%Specificity 48.1%
<table><tr><td></td><td>Reference test +</td><td>Reference test -</td><td>Total</td></tr></table></td><td>Limitations Risk of bias assessed using QUADAS-II
<u>DOMAIN 1: PATIENT SELECTION</u>
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? unclear
2. Was a case-control design avoided? yes
3. Did the study avoid inappropriate</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Study dates
January 2001 - June 2002

Source of funding
National Center for Research Resources</td>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>Index test +</td><td>152</td><td>27</td><td></td></tr>
<tr><td>Index test -</td><td>16</td><td>25</td><td></td></tr>
<tr><td>Total</td><td>168</td><td>52</td><td>220</td></tr>
</table>
<u>Cut off ~0.30 (300mg/g)</u>
Sensitivity 81.0%Specificity 55.8%
<table>
<tr><td></td><td>Reference test +</td><td>Reference test -</td><td>Total</td></tr>
<tr><td>Index test +</td><td>136</td><td>23</td><td></td></tr>
<tr><td>Index test -</td><td>32</td><td>29</td><td></td></tr>
<tr><td>Total</td><td>168</td><td>52</td><td>220</td></tr>
</table>
<u>Cut off ~0.39 (390mg/g)</u>
Sensitivity 72.6%Specificity 73.1%
</td>
<td>exclusions? yes

Could the selection of patients have introduced bias? RISK: LOW

B. CONCERNS REGARDING APPLICABILITY Is there concern that the included patients do not match the review question? CONCERN: LOW

<u>DOMAIN 2: INDEX TESTS</u>
A. RISK OF BIAS

1. Were the index test results interpret</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					ed without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? unclear **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index

	Reference test +	Reference test -	Total
Index test +	122	14	
Index test -	46	38	
Total	168	52	220

Cut off ~0.40 (400mg/g)
Sensitivity 71.4%Specificity 76.9%

	Reference test +	Reference test -	Total
Index test +	120	12	
Index test -	48	40	
Total	168	52	220

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Cut off ~0.50 (500mg/g)
Sensitivity 63.1%Specificity 82.7%
<table>
<tr><td></td><td>Reference test +</td><td>Reference test -</td><td>Total</td></tr>
<tr><td>Index test +</td><td>106</td><td>9</td><td></td></tr>
<tr><td>Index test -</td><td>62</td><td>43</td><td></td></tr>
<tr><td>Total</td><td>168</td><td>52</td><td>220</td></tr>
</table></td><td>test, its conduct, or interpretation differ from the review question? CONCERN: LOW

<u>DOMAIN 3: REFERENCE STANDARD</u>
A. RISK OF BIAS

1. Is the reference standard likely to correctly classify the target condition? yes
2. Were the reference standard results interpreted without knowledge of the</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					results of the index test? unc lear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					DOMAIN 4: FLOW AND TIMING **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? Yes 4. Were all patients included in the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					analysis? yes **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Dwyer, B. K., Gorman, M., Carroll, I. R., Druzin, M., Urinalysis vs urine protein - Creatinine ratio to predict significant proteinuria in pregnancy, Journal of Perinatology, 28, 461-467, 2008 **Ref Id** 838685 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study	**Sample size** n=116 (n=60 proteinuria<300mg/24hr ; n=56 proteinuria≥300mg/24hr) **Characteristics** <u>women with proteinuria≥300mg/day</u> age: 30.8 SD 6.5 years SBP: 143.3 SD 16.3 mmHg DBP: 91.5 SD 12.8 mmHg <u>women with proteinuria< 300mg/day</u> age: 30.8 SD 6.2 years SBP: 141.4 SD 13.1 mmHg	**Tests** Index test: spot urine PCR (prior to 24 hr collection if possible) Reference test: 24 hr urine collection	**Methods** Urine PCR were usually obtained immediately before the 24-h urine collection was begun. If that sample was not available at the time of enrolment, a sample was obtained immediately after the 24-h collection. Samples were collected via clean catch unless the membranes had been ruptured, in which case specimens were obtained by catheter Urinary protein and creatinine were measured using Synchron LX Systems (Beckman Coulter Inc., Fullerton, CA, USA), which uses the pyrogallol red/molybdate and Jaffe rate methods	**Results** n=60 proteinuria<300mg/24hr; n=56 proteinuria≥300mg/24hr **AUC=0.89 (0.83-0.95)** <u>cut-offs: ≥0.15 (maximise sensitivity), ≥0.28 (max specificity), ≥0.19 (optimise sens and spec)</u> 0.15: Sens 0.96 (0.87 - 0.99); spec 0.53 (0.40 - 0.66); [TP 54; FP 28; FN 2; TN 32; back calculated by NGA] **0.19: 0.89 (0.78 - 0.96); 0.70 (0.59-0.83); [TP 50; FP 18; FN 6; TN 42; back calculated by NGA]** 0.28: 0.66 (0.52 -0.78); 0.95 (0.86 - 0.99); [TP 37; FP 3; FN 19; TN 57; back calculated by NGA]	**Limitations** **Risk of bias assessed using QUADAS-II** **<u>DOMAIN 1: PATIENT SELECTION</u>** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To compare the urine protein–creatinine ratio with urinalysis to predict significant proteinuria (≥300 mg per day) **Study dates** September 2002 - March 2004 **Source of funding** supported by the Department of Gynecology and Obstetrics, Stanford University.	DBP: 89.3 SD 11.3 mmHg **Inclusion Criteria** all women being evaluated for pre-eclampsia, regardless of the alerting sign or symptom, suspected severity or comorbid conditions **Exclusion Criteria** urinalysis contained >10 WBCs per h.p.f., if a catheter was not used after membrane rupture or if an outpatient 24-h urine collection was incomplete				control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **DOMAIN 2: INDEX TESTS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. RISK OF BIAS 1. Were the index test results interpreted without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? no **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					B. CONCERNS REGARDING APPLICABILITY Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition ? yes 2. Were the referenc

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					e standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard ? Yes 4. Were all patients included in the analysis? yes **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Eslamian, L., Behnam, F., Tehrani, Z. F., Jamal, A., Marsoosi, V., Random urine protein creatinine ratio as a preadmission test in hypertensive pregnancies with urinary protein creatinine ratio, Acta Medica Iranica, 49, 81-4, 2011 **Ref Id** 658175	**Sample size** n=113 enrolled; n=100 in final analysis (n=46 proteinuria≥300mg/day; n=4 proteinuria≥2000mg/day) **Characteristics** age: 30.6 (19-44) years gestational age: 31 (22-39) weeks SBP: 145 (120-180) mmHg	**Tests** Index test: spot urine PCR Reference test: 24 hr urine collection (proteinuria ≥300mg/day)	**Methods** Random urine sample for assessing PCR was obtained after admission, excluding the 1st voided morning urine. 24h urine collection started from 8 AM on the morning following admission. patients were on moderate bed rest and were recommended to have a left lateral decubitis position when in bed. They were allowed to spend a few hours out of bed.	**Results** n=46 proteinuria≥300mg/day; n=54 proteinuria <300mg/day AUC: 0.926 (95%CI 0.854-0.995) cut off: 0.22mg/mg: sens 0.879; spec 0.926 [TP 40; FP 4; FN 6; TN 50; back calculated by NGA]	**Limitations Risk of bias assessed using QUADAS-II <u>DOMAIN 1: PATIENT SELECTION</u> A. RISK OF BIAS** 1. Was a consecutive or random sample

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Iran **Study type** Case-series **Aim of the study** to determine whether random urine PCR can be used to rule out significant proteinaria (≥300mg/dl) and to use it as a pre admission test in suspected cases of PE **Study dates** October 2007 - January 2009 **Source of funding** Not reported	DBP: 91.9 (90-110) mmHg **Inclusion Criteria** All pregnant women with new onset hypertension ≥140/90 mmHg after GA of 20 weeks **Exclusion Criteria** • Women suspected of having urinary tract infection • Chronic hypertension before pregnancy or in the first half of pregnancy • Pre-existing renal disease with proteinuria • Women with diabetic nephropathy		Urine protein and creatinine were measured by Biosystems (Barcelona, Spain).		of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? no **Could the conduct or interpretatio**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					n of the index test have introduced bias? RISK: UNCLEAR **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					classify the target condition ? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard ? yes 3. Did patients receive the same reference standard ? Yes 4. Were all patients included in the analysis? No – n=100/113; 88% (113 enrolled, excluded due to inadequate 24 hour collection) **Could the patient flow have introduced bias? RISK: LOW**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Other information
Full citation Kucukgoz Gulec, U., Sucu, M., Ozgunen, F. T., Buyukkurt, S., Guzel, A. B., Paydas, S., Spot Urine Protein-to-Creatinine Ratio to Predict the Magnitude of 24-Hour Total Proteinuria in Preeclampsia of Varying Severity, Journal of Obstetrics & Gynaecology Canada: JOGC, 21, 21, 2017 **Ref Id** 658938 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study **Aim of the study** assess the diagnostic accuracy of spot urine PCR for ascertaining the magnitude of proteinuria in women with PE of varying severity	**Sample size** n=276 enrolled; n=205 in final analysis (n=41/205 proteinuria<300mg/24hrs; n=164/205 proteinuria≥300mg/24hrs) **Characteristics** age: 30.1 SD 7.4 years; median 30.0 (range 16-50) GA: 33.7 SD 4.6 weeks; median 34 (range 20-41) **Inclusion Criteria** pregnant women being evaluated for PE **Exclusion Criteria** concurrent diseases: • urinary tract infection, • chronic hypertension,	**Tests** Index test: spot clean catch urine PCR (immediately after 24 hr urine collection) reference test: 24 hour urine collection (proteinuria≥300mg/24hr)	**Methods** Evaluation of PCR did not change treatment/management. Urinary protein and creatinine were measured by the Pyrogallol Red and picrate methods, respectively (Beckman Coulter DXC 800, Beckman Coulter, Krefeld, Germany).	**Results** n=164/205 proteinuria≥300mg/24hrs <u>PCR cut-off:</u> 0.53mg/mg: sensitivity 81.2%; specificity 93.2%; AUC 0.91; [TP 133; FP 3; FN 31; TN 38; back calculated by NGA] 0.28mg/mg: sensitivity 82%; specificity 71%; AUC 0.78; [TP 134; FP 12; FN 30; TN 29; back calculated by NGA]	**Limitations Risk of bias assessed using QUADAS-II** **<u>DOMAIN 1: PATIENT SELECTION</u>** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates May 2011 - March 2013 **Source of funding** Not reported	• diabetes mellitus • pre-existing renal disease • systemic diseases such as systemic lupus erythematosus				exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpret

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					ed without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? no **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition ? yes 2. Were the reference standard results interpreted without knowledge of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. RISK OF BIAS 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? Yes 4. Were all patients included in the analysis? No – included

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					n=205/276; 74% (excluded because 24-hour urine was not collected and/or PCR was not measured) **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Kyle, P. M., Fielder, J. N., Pullar, B., Horwood, L. J., Moore, M. P., Comparison of methods to identify significant proteinuria in pregnancy in the outpatient setting, BJOG: An International Journal of Obstetrics and Gynaecology, 115, 523-527, 2008	**Sample size** n=188 recruited; n=150 in final analysis (at testing, n=13 had proteinuria≥300mg/24hr) **Characteristics** *median (range)*	**Tests** Index test: spot urine PCR, and spot urine ACR Reference test: 24 hr urine collection (after spot tests)	**Methods** Spot urine tests before 24 hr urine collection. First morning void discarded. Participants were encouraged to complete the 24-hour specimen as soon as possible and were given up to 3 days to do so. Mid-stream urine sample was separated into three aliquots for testing including (1) PCR, (2)	**Results** n=13/150 had proteinuria≥300mg/day **<u>ACR cut-offs: ≥8.0; ≥3.5, ≥2.0 mg/mmol</u>** AUC: 0.991 (95%CI 0.974 - 1.000) ≥2.0: sens 100 (75.3-100); spec 67.9 (59.4-75.6); LR+ 3.1 (2.4-4.0); LR- 0.0 (-); [TP 13; FP 44; FN 0; TN 93]; back calculated by NGA] ≥3.5: sens 100 (75.3-100); spec 87.6 (80.9-92.6); LR+ 8.1 (5.2-	**Limitations** **Risk of bias assessed using QUADAS-II** **<u>DOMAIN 1: PATIENT SELECTION</u>** **A. RISK OF BIAS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 838719 **Country/ies where the study was carried out** New Zealand **Study type** Prospective cohort study **Aim of the study** examine the efficacy of the ACR (DCA 2000) in the detection of significant proteinuria when performed in outpatient antenatal clinics compared with the automated dipstick, PCR, and the 24-hour urine protein **Study dates** Not reported **Source of funding** University of Otago Grant 2005, Canterbury District Health Board Research Grant 2005, and Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)	GA at testing:34.0 (20.1–39.7) weeks SBP: 120 (90–172) mmHg DBP: 75.5 (50–110) mmHg **Inclusion Criteria** Women greater than 20 weeks of gestation (single or multiple gestation) attending the high-risk obstetric medical antenatal clinic **Exclusion Criteria** positive urine culture for urinary tract infection, underlying proteinuric renal disease, diabetes with an abnormal ACR in the first trimester		ACR (DCA 2000), and (3) culture and sensitivity: A spot sample for a PCR was sent to Canterbury Health Laboratories (Abbott Ci8200 Analysers; Chicago, IL, USA). This test quantifies the amount of proteinuria and standardises it against the creatinine concentration. These results take up to 2–4 hours to obtain. A spot sample for an ACR was performed in the antenatal clinic using the DCA 2000 (Bayer Healthcare LLC). The DCA 2000 is a point of care system used to estimate the ACR from a small (40 ml) sample of urine.	12.6); LR- 0.0 (-); [TP 13; FP 17; FN 0; TN 120; back calculated by NGA] **≥8.0: sens 100 (75.3-100); spec 96.4 (91.7-98.8); LR+ 27.4 (11.6-64.8); LR- 0.00 (-) [TP 13; FP 5; FN 0; TN 132; back calculated by NGA]** **<u>PCR ≥30.0mg/mmol</u>** AUC: 0.988 (95%CI 0.971 - 1.000) **≥30.0:** sens 92.3 (64.0-99.8); spec 97.1 (92.7-99.2); LR+ 31.6 (11.9-84.1); LR- 0.1 (0.01-0.52); [TP 12; FP 4; FN 1; TN 133; back calculated by NGA]	1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABIL**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Trainee Scholarship awarded to JNF 2005					**ITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard? unclear 2. If a threshold was used, was it pre-

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					specified ? no **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **DOMAIN 3: REFERENCE STANDARD** **A. RISK OF BIAS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					B. CONCERNS REGARDING APPLICABILITY Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard ? yes 2. Did all patients receive a reference standard ? yes 3. Did patients receive the same reference standard ? Yes 4. Were all patients included in the analysis? No – included n=150/188; 80% (35 excluded for incomplete 24 hour urine, 3 for having UTI)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the patient flow have introduced bias? RISK: LOW **Other information**
Full citation Lamontagne, A., Cote, A. M., Rey, E., The urinary protein-to-creatinine ratio in Canadian women at risk of preeclampsia: does the time of day of testing matter?, Journal of Obstetrics & Gynaecology Canada: JOGC, 36, 303-8, 2014 **Ref Id** 658283 **Country/ies where the study was carried out** Canada **Study type** Prospective cohort study **Aim of the study** determine the performance of a protein-to-creatinine ratio threshold of 30mg/mmol	**Sample size** n=119 samples; n=91 in final analysis (n=43 with proteiuria≥300mg/day) **Characteristics** age: 31.8 SD 5.8 years GA at testing: 32.3 SD 3.7 weeks **Inclusion Criteria** older than 18 years, in their second or third trimester of pregnancy, ambulatory, and had an indication for a 24-hour urine collection as part of investigation for pre-eclampsia **Exclusion Criteria**	**Tests** Index test: urine PCR provided at any moment during the day Reference test: 24 hour urine collection (proteinuria ≥300mg/24hrs)	**Methods** Urinalysis, urine culture, and a PCR calculation were performed on the same urine sample provided at any moment during the day. The 24-hour urine collection began immediately afterwards to evaluate 24-hour excretion of protein and creatinine. The physician providing management was blinded to the protein-to-creatinine ratio result. Protein concentration in the urine was determined by a colorimetric method using pyrogallol red-molybdate. Urinary and plasma creatinine concentrations were measured with the Jaffé method. All analyses were performed by the Beckman Coulter multianalyzer with the Synchron LX system (Beckman Coulter Canada LLP, Mississauga, ON). The protein-to-creatinine ratio was	**Results** proteinuria≥300mg/day: n=43/91 PCR cut-off: 30mg/mmol All samples (n=91) **AUC: 0.99 (95%CI 0.97 to 1.0); Sens 81% (67 to 92); Spec 98% (89 to 100); LR+ 39 (6 to 273); LR- 0.19 (0.1 to 0.4); [TP 35; FP 1; FN 8; TN 47; back calculated by NGA]** First morning sample (n=30; no detail on number with +ve ref standard therefore cannot back calculate) AUC: 0.94 (0.86 to 1.0); Sens 58 (28 to 85); Spec 93 (66 to 100); LR+ 8 (1.2 to 57.3); LR- 0.45 (0.2 to 0.9) All samples except first morning void (n=61; no detail on number with +ve ref standard therefore cannot back calculate) AUC: 1.0 (0.99 to 1.0); Sens 90% (74 to 98); Spec 100% (90 to 100); LR+ not calc; LR- 0.1 (0.03 to 0.3)	**Limitations Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
in pregnant women investigated for hypertension according to the time of day of the sample **Study dates** November 2005 - November 2006 **Source of funding** Not reported	serum creatinine level > 150 µmol/L, history of renal transplant, pre-existing microalbuminuria or proteinuria, macroscopic hematuria, known urinary tract infection, and incomplete urine collections, defined by a urinary creatinine < 10 mmol/kg of pre-pregnancy weight		expressed in mg/mmol (mg/mmol = mg/mg × 0.113).		3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **DOMAIN 2: INDEX TESTS** **A. RISK OF BIAS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					1. Were the index test results interpreted without knowledge of the results of the reference standard? yes 2. If a threshold was used, was it pre-specified? yes **Could the conduct or interpretation of the index test have introduced bias?** **RISK: LOW** **B. CONCERNS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					REGARDING APPLICABILITY Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					results interpreted without knowledge of the results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					4. Were all patients included in the analysis? No – included n=91/119; 76% (exclusions because of labour (n = 6), incomplete 24-hour collection (n = 2), renal insufficiency (n = 1), urinary tract infection (n = 1), previous collection in the study (n = 6), and laboratory problems (form

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					error, n = 12)) **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Leanos-Miranda, A., Marquez-Acosta, J., Romero-Arauz, F., Cardenas-Mondragon, G. M., Rivera-Leanos, R., Isordia-Salas, I., Ulloa-Aguirre, A., Protein:creatinine ratio in random urine samples is a reliable marker of increased 24-hour protein excretion in hospitalized women with hypertensive disorders of pregnancy, Clinical Chemistry, 53, 1623-8, 2007 **Ref Id** 658946 **Country/ies where the study was carried out** Mexico	**Sample size** n=1198 enrolled; n=927 in final analysis (proteinuria≥300mg/day n=282) **Characteristics** age: 28.6 (6.2) years (range 14–45 years) GA: 33 weeks (range 21–40 weeks) **Inclusion Criteria** GA≥20 weeks had new onset of hypertension with or without suspicion of pre-eclampsia or chronic hypertension (before 20 weeks of gestation) with suspected	**Tests** Index test: random urine sample for PCR (before or after start of 24 hr collection; not first voided sample) Reference test: 24 hour urine collection	**Methods** Urine protein was measured by the Bradford method (Bio-Rad Protein Assay Kit, Bio-Rad Laboratories) using BSA (Bio-Rad) as a calibrator. Assay manually as described by the manufacturer. Urine creatinine was measured by the modified kinetic Jaffe reaction in a 96-well plate with a filter at 490 nm.	**Results** proteinuria≥300mg/day n=282/927 PCR cut-off: 30mg/mmol AUC 0.998 (95%CI 0.993-1.0); Sens 98.2% (95.9-99.4); spec 98.8% (97.6-99.5); LR+ 79.2 (39.8-157.7); LR- 0.02 (0.008-0.043); FP 8; FN 5; [TP 277; TN 637; back calculated by NGA] proteinuria≥2g/day PCR cut off: 1.45 AUC 0.998 (0.993-1.0); sens 100% (95.6-100); spec 97% (95.7-98.1); LR+ 33.8	**Limitations Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Prospective cohort study **Aim of the study** assess whether measurement of urine PCR in a single urine specimen in clinical practice provides a reliable estimate of significant proteinuria (≥300mg/24hrs) in women with hypertensive disorders of pregnancy **Study dates** Not reported **Source of funding** Grant funding/support: This study was supported by Grant FP-2005/1/I/119 (to A.L.-M.) from the Fondo para el Fomento de la Investigacion-IMSS, Mexico	superimposed pre-eclampsia. hospitalized pregnant women (GA≥20 weeks) where a hypertensive disorder of pregnancy was ruled out were also included in the study **Exclusion Criteria** Not reported				avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. RISK OF BIAS 1. Were the index test results interpreted without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? unclear **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					B. CONCERNS REGARDING APPLICABILITY Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition ? yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					reference standard? Yes 4. Were all patients included in the analysis? No – included N=927/1198; 77% (271 excluded for inadequate 24 hour urine collection) **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation	**Sample size**	**Tests**	**Methods**	**Results**	**Limitations**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Mohseni, S. M., Moez, N., Naghizadeh, M. M., Abbasi, M., Khodashenas, Z., Correlation of random urinary protein to creatinine ratio in 24-hour urine samples of pregnant women with preeclampsia, Journal of Family & Reproductive Health, 7, 95-101, 2013 **Ref Id** 658966 **Country/ies where the study was carried out** Iran **Study type** Prospective cohort study **Aim of the study** determine the value of random urinary protein to creatinine ratio (UPCR) for diagnosis of proteinuria in pregnant women with PE **Study dates** May 2006 - May 2008 **Source of funding**	n=66 (proteinuria≥300mg n=49) **Characteristics** age: 24.45 SD 7.6 years (range 14-46) GA: 28.18 SD 2.75 weeks (24-35) **Inclusion Criteria** GA≥24 weeks, diagnosed with increase in blood pressure after 20th week of pregnancy to≥140/90mm Hg, and subjected to a 24-hour urine protein assay **Exclusion Criteria** chronic hypertension, diabetic mellitus, kidney disease and urinary infection	Index test: samples at 10am and 4pm (first voided sample discarded) Reference test: 24 hr urine collection (proteinuria≥300mg/24hrs)	Urine creatinine was assayed using Jaffe reaction and picric acid reagent.(Roche, Germany). Proteinuria in the 24-hour urine collection was assayed using the turbidimetric test along with the Trichloro - acetic acid reagent. All reagents were prepared by the Roche, Germany Company.	proteinuria≥300mg n=49/66 <u>PCR cut offs at 10am:</u> AUC 0.890 SE 0.055 0.299: TN 13; FN 2; FP 6; TP 46 0.349: 14; 3; 5; 45 0.399: 14; 4; 5; 44 0.449: 16; 6; 3; 42 0.499: 16; 6; 3; 42 0.549: 16; 8; 3; 40 **0.595mg: sens 91.67%; spec 94.74% [TP 45; FP 1; FN 4; TN 16; back calculated by NGA]** 0.599: 16; 8; 3; 40 <u>PCR cut offs at 4pm:</u> AUC 0.932 SE 0.049 0.399: TN 15; FN 2; FP 4; TP 46 0.449: 16; 2; 3; 46 **0.470mg: sens 87.5%; spec 84.21% [TP 43; FP 3; FN 6; TN 14; back calculated by NGA]** 0.499: 16; 3; 3; 45 0.549: 17; 4; 2; 44 0.599: 18; 4; 1; 44 0.649: 18; 5; 1; 43 0.699: 18; 8; 1; 40 0.749: 18; 12; 1; 36 0.799: 18; 13; 1; 35	**Risk of bias assessed using QUADAS-II** **<u>DOMAIN 1: PATIENT SELECTION</u>** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Not reported					**introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the referenc

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					e standard ? unclear 2. If a threshold was used, was it pre-specified ? no **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					1. Was there appropriate interval between index tests and reference standard ? yes 2. Did all patients receive a reference standard ? yes 3. Did patients receive the same reference standard ? Yes 4. Were all patients included in the analysis? yes **Could the patient flow**

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>have introduced bias? RISK: LOW

Other information</td></tr>
<tr><td>Full citation

Nisar, N., Akhtar, N., Dars, S., Diagnostic accuracy of spot urine protein-creatinine ratio in women with pre-eclapmsia, Medical Forum Monthly, 28, 6-10, 2017

Ref Id

838736

Country/ies where the study was carried out

India

Study type

Descriptive

Aim of the study
to determine the diagnostic accuracy of spot urine PCR in women with PE compared with 24-hour urine protein excretion

Study dates</td><td>Sample size
n=404 (n=246 PE according to 24hr collection; n=358 PE according to PCR)

Characteristics
age: 27.08 SD 5.84 years (range 16-40)
GA at testing: 36.26 SD 4.59 weeks
SBP: 161.68 SD 19.59 mmHg
DBP: 104.70 SD 12.65 mmHg

Inclusion Criteria
GA≥20 weeks, SBP≥140mmHg, or DBP≥90mmHg

Exclusion Criteria
women with ruptured membranes, and who delivered during urine</td><td>Tests
Index test: spot mid-stream urine sample (taken before 24 hr collection; PCR cut off set at 0.2)
Reference test: 24 hour urine collection: 8am to 8am</td><td>Methods
Spot urine sample prior to 24 hr collection.
Total protein concentration was measured by biuret colorimeter assay and creatinine level measured by modified Jaffe test.
If PE was confirmed, women were treated.</td><td>Results
n=246/404 PE (≥300mg/24hr) according to 24hr collection
PCR cut off 0.2: Sensitivity 0.975; Specificity 0.253
<table><tr><td></td><td>24hr +ve</td><td>24hr -ve</td><td>total</td></tr><tr><td>PCR +ve</td><td>240</td><td>118</td><td>358</td></tr><tr><td>PCR -ve</td><td>6</td><td>40</td><td>46</td></tr><tr><td>total</td><td>246</td><td>158</td><td>404</td></tr></table></td><td>Limitations Risk of bias assessed using QUADAS-II
<u>DOMAIN 1: PATIENT SELECTION</u>
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? yes
2. Was a case-control design avoided? yes
3. Did the study avoid</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
20 February 2015 - 19 February 2016 **Source of funding** Not reported	collection, women with urinary tract infection and associated medical disorders (renal disease, diabetes mellitus), women who had bedrest longer than 24 hours at presentation				inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **DOMAIN 2: INDEX TESTS** **A. RISK OF BIAS** 1. Were the index test

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					results interpreted without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? yes **Could the conduct or interpretation of the index test have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **DOMAIN 3: REFERENCE STANDARD** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition ? yes 2. Were the reference standard results interpreted without

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					DOMAIN 4: FLOW AND TIMING **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? Yes 4. Were all patients included in the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					analysis? yes **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Park, Jung-Hwa, Chung, Dawn, Cho, Hee-Young, Kim, Young-Han, Son, Ga-Hyun, Park, Yong-Won, Kwon, Ja-Young, Random urine protein/creatinine ratio readily predicts proteinuria in preeclampsia, Obstetrics & gynecology science, 56, 8-14, 2013 **Ref Id** 813552 **Country/ies where the study was carried out** South Korea **Study type**	**Sample size** n=140 evaluated; n=79/140 assigned to PCR or 24 hr collection; n=33/79 excluded; n=46 where both 24 hr and spot urine collection were available (proteinuria<300mg/24hrs n=2/46; proteinuria 300mg-5000mg/24hrs n=38/46; proteinuria≥5g/24hrs n=6/46) **Characteristics** age: 33.2 SD 4.8 years (range 19-43) GA at delivery: 33.3 SD 3.4 weeks (range 27-40)	**Tests** Index test: random urine PCR using a catheter (before 24 hour collection started) Reference test: 24 hour urine collection (proteinuria≥300mg/24hrs)	**Methods** Urine collected via catheterization for the random urine PCR and the urinary dipstick test. Then, a 24-hour urine was collected via a clean catch. Random urine PCR was determined by a Hitachi 7180 Autoanalyzer (Hitachi, Tokyo, Japan)	**Results** **proteinuria<300mg/24hrs n=2/46; proteinuria≥300mg/24hrs n=44/46** AUC 0.958 (95%CI 0.903-1.0): optimal cutoff 0.63 Sensitivity 87.1%; Specificity 100%; [TP 38; FP 0; FN 6; TN 2; back calculated by NGA] **proteinuria≥5g/24hrs n=6/46: optimal cut-off 4.68** AUC 0.921 (1.074-2.002 [as reported in study]); sensitivity 100%; specificity 85%; [TP 6; FP 6; FN 0; TN 34; back calculated by NGA]	**Limitations** **Risk of bias assessed using QUADAS-II** **<u>DOMAIN 1: PATIENT SELECTION</u>** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Retrospective cohort study **Aim of the study** assess the diagnostic accuracy of random urine PCR for prediction of significant proteinuria in PE as an alternative to the time-consuming 24-hour urine protein collection **Study dates** January 2006 - June 2011 **Source of funding** National Research Foundation of Korea Grant funded by the Korean Government (2010-0010727)	SBP at admission: 157.8 SD 20.7 mmHg (range 108.0-200.0) DBP at admission: 97/5 SD 9.5 mmHg (range 74.0-120.0) **Inclusion Criteria** Women with symptoms of PE and more than one clinical finding: hypertension, edema accompanied by rapid weight gain with or without headache, and new-onset proteinuria on a urinary dipstick test **Exclusion Criteria** Concurrent preexisting renal disease such as immunoglobulin (Ig) A nephropathy				control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					<u>DOMAIN 2: INDEX TESTS</u> **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? no **Could the conduct or interpretation of the index test have introduced**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					bias? RISK: UNCLEAR **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					condition ? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					defined by the reference standard does not match the review question? CONCERN: UNCLEAR - confusion over data presented **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard ? yes 3. Did patients receive the same reference standard ? Yes 4. Were all patients included in the analysis? No - included n=46/140 ; 33% (n=140 evaluated for PE; n=79/140 assessed using PCR or 24 hr collection ; n=33/79 excluded for incomplete 24hr urine – labour started)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the patient flow have introduced bias? RISK: LOW **Other information**
Full citation Rizk, D. E. E., Agarwal, M. M., Pathan, J. Y., Obineche, E. N., Predicting proteinuria in hypertensive pregnancies with urinary protein-creatinine or calcium-creatinine ratio, Journal of Perinatology, 27, 272-277, 2007 **Ref Id** 776570 **Country/ies where the study was carried out** United Arab Emirates **Study type** Prospective cohort study **Aim of the study**	**Sample size** n=95 recruited; n=83 in final analysis (n=51 proteinuria≥300mg/24hrs) **Characteristics** age: 29.4 SD 6.6 years (range 16-45) GA at sampling: 32.1 SD 1.6 weeks (range 22-38) SBP at sampling: 153.3 SD 12.9 mmHg (range 130-170) DBP at sampling: 97.2 SD 8.2 mmHg (range 90-110) **Inclusion Criteria** Attended study hospital for management of	**Tests** Index test: spot clean-catch and midstream voided urine sample for PCR (not first morning void) immediately before 24hr collection started Reference test: 24 hr urine collection (8am on morning after admission to 8am following day)	**Methods** None of the spot samples was first-voided morning urine. Spot urine test immediately before 24hr collection. Urinary protein, creatinine and calcium concentrations were measured by a standard technique using the Beckman Synchron (Beckman-Coulter Instruments, Brea, CA, USA). Individual results of spot urinary assays were not made available to the obstetricians responsible for patient care, or the lab technicians and study investigators.	**Results** n=51/83 proteinuria≥300mg/24hrs; n=4/83 proteinuria>5g/24hrs **AUC=0.82 (95%CI 0.72- 0.91)** PCR cut-offs: 0.19, 0.36, 0.55, 0.86, 1.4 **>0.19: n=51; Sens 80.4%; Spec 68.8%; LR+ 2.57; LR- 3.51; [TP 41; FP 10; FN 10; TN 22; back calculated by NGA]** >0.36: n=42; 68.6%; 78.1%; 3.14; 2.49; [TP 35; FP 7; FN 16; TN 25; back calculated by NGA] >0.55: n=31; 52.9%; 87.5%; 4.24; 1.86; [TP 27; FP 4; FN 24; TN 28; back calculated by NGA] >0.86: n=24; 43.1%; 93.8%; 6.90; 1.65; [TP 22; FP 2; FN 29; TN 30; back calculated by NGA] >1.4: n=19; 35.3%; 96.9%; 11.29; 1.50; [TP 18; FP 1; FN 33; TN31; back calculated by NGA]	**Limitations Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Evaluate the value of random urinary PCR and calcium-creatinine (CaCr) ratios to predict 24-h proteinuria in hypertensive pregnancies **Study dates** 1 Novemeber 2005 - 28 February 2006 **Source of funding** Not reported	hypertension in study period **Exclusion Criteria** Women with intrauterine fetal death, coexisting or recurrent urinary tract infection and current diuretic therapy within 7 days of the hospital visit and immuno-compromised patients. Women who have been placed on long-term bed rest at home or strict bed rest in another hospital for more than 36 h before admission				avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **DOMAIN 2: INDEX TESTS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. RISK OF BIAS 1. Were the index test results interpreted without knowledge of the results of the reference standard ? yes 2. If a threshold was used, was it pre-specified ? no **Could the conduct or interpretation of the index test have introduced bias?** **RISK: LOW**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					B. CONCERNS REGARDING APPLICABILITY Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition ? yes 2. Were the referenc

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					e standard results interpreted without knowledge of the results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard ? Yes 4. Were all patients included in the analysis? No – included n=83/95; 87% (exclusions: n=7 for inadequate 24 hour urine sample; 5 women refused to participate) **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation	**Sample size**	**Tests**	**Methods**	**Results**	**Limitations**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Rodriguez-Thompson, D., Lieberman, E. S., Use of a random urinary protein-to-creatinine ratio for the diagnosis of significant proteinuria during pregnancy, American Journal of Obstetrics & Gynecology, 185, 808-11, 2001 **Ref Id** 659003 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** evaluate whether a random urinary PCR is a clinically useful predictor of significant proteinuria (300mg/24 hour) **Study dates** Not reported **Source of funding** Not reported	n=138 (n=69 proteinuria ≥300mg/24hrs) **Characteristics** median age: 30 years (range 16-49) **Inclusion Criteria** Had both random PCR and 24 hour urine collection **Exclusion Criteria** Patients with pre-existing intrinsic renal disease	Index test: random urinary PCR (before 24 hr collection, and not first morning void) Reference test: 24 hr urine collection (proteinuria≥300mg/24hrs)	Medical records searched for completion of both 24 hour urine collection and random urinary PCR. All random samples collected before 24 hour collection, not first voided. Urinary protein concentration was determined with the use of the Dimension (Dade Behning, Inc, Nework, Del) clinical chemistry system UCFP method, which uses the pyrogallol red-molybdate method; urinary creatinine test was performed with the use of the Dimension (Dade Behning) clinical chemistry system CREA method, which uses a modified Jaffe reaction. Results could be accessed by the clinicians, but no clinical decision was based on the random urine PCR during the study period	n=69/138 proteinuria ≥300mg/24hrs AUC 0.9143 (95%CI 0.87-0.96) PCR cut-offs: 0.14: sens 1.00; spec 0.51; [TP 69; FP 34; FN 0; TN 35; back calculated by NGA] 0.15: 0.99; 0.51; [TP 68; FP 34; FN 1; TN 35; back calculated by NGA] 0.16: 0.99; 0.62; [TP 68; FP 26; FN 1; TN 43; back calculated by NGA] 0.17: 0.94; 0.64; [TP 65; FP 25; FN 4; TN 44; back calculated by NGA] 0.18: 0.90; 0.65; [TP 62; FP 24; FN 7; TN 45; back calculated by NGA] **0.19: sens 90%; spec 70%; FN 7; FP 21; [TP 62; TN 48; calculated by NGA]** 0.20: 0.88; 0.72; [TP 61; FP 19; FN 8; TN 50; back calculated by NGA] 0.21: 0.88; 0.75; [TP 61; FP 17; FN 8; TN 52; back calculated by NGA]	**Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					introduced bias? RISK: LOW **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the referenc

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					e standard ? unclear 2. If a threshold was used, was it pre-specified ? no **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear - clinicians had

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					access to the results, but were not used for clinical decisions (if checked) **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					4. Were all patients included in the analysis? yes **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Saudan, P. J., Brown, M. A., Farrell, T., Shaw, L., Improved methods of assessing proteinuria in hypertensive pregnancy, British Journal of Obstetrics & Gynaecology, 104, 1159-64, 1997 **Ref Id** 659007 **Country/ies where the study was carried out** Australia **Study type**	**Sample size** n=103 enrolled; n=100 in final analysis (14% had proteinuria≥300mg/24hrs and PCR>380mg/mmol) **Characteristics** Not reported **Inclusion Criteria** Pregnant women admitted to hospital or pregnancy day assessment unit for	**Tests** Index test: spot midstream urine sample usually (not always) obtained in the morning (before 24 hr collection started) Reference test: 24 hour urine collection (proteinuria≥300mg/24hrs)	**Methods** Urine protein was measured by a benzethoniwn chloride turbidometric method and urine creatinine by the Jaffe method, both using an Hitachi 911 autoanalyser (Boehringer Manheim)	**Results** n=14/100 proteinuria≥300mg/24hrs PCR cut-off: 20: sens 100%; spec 69%; [TP 14; FP27; FN 0; TN 59; back calculated by NGA] 25: 95%; 84%; [TP 13; FP 14; FN 1; TN 72; back calculated by NGA] "optimal" 30mg/mmol: 93%; 92%; [TP 13; FP 7; FN 1; TN 79; back calculated by NGA] 35: 83%; 95%; [TP 12; FP 4; FN 2; TN 82; back calculated by NGA] 40: 81%; 97%; [TP 11; FP 3; FN 3; TN 83; back calculated by NGA] 45: 72%; 100%; [TP 10, FP 0; FN 4; TN 86; back calculated by NGA]	**Limitations Risk of bias assessed using QUADAS-II DOMAIN 1: PATIENT SELECTION A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Prospective cohort study **Aim of the study** determine whether use of an automated urinalysis device will improve the accuracy of detecting proteinuria, and whether spot urine protein to creatinine ratio will provide accurate quantitation of proteinuria in hypertensive pregnant women **Study dates** "a six month interval" **Source of funding** Division of Medicine and Southpath Pathology services, St George Hospital. Lead author was a recipient of the fonds de perfectionnement from the University Hospital, Geneva, Switzerland	management of their hypertensive disorders **Exclusion Criteria** Not reported				2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					DOMAIN 2: INDEX TESTS **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? no **Could the conduct or interpretation of the index test have introduced**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					bias? RISK: UNCLEAR **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					condition ? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					receive the same reference standard? Yes 4. Were all patients included in the analysis? No – included n=100/103; 97% (only those with both 24 hour urine and PCR analysis) **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Stout, M. J., Scifres, C. M., Stamilio, D. M., Diagnostic	**Sample size** n=356 (proteinuria≥300mg/day n=144)	**Tests** Index test: urine PCR sample prior to 24 hour collection	**Methods** Laboratory methodology used end-point assay colorimetric	**Results** proteinuria≥300mg/day n=144/356 AUC: 0.82 PCR cut-offs	**Limitations Risk of bias assessed**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
utility of urine protein-to-creatinine ratio for identifying proteinuria in pregnancy, Journal of Maternal-Fetal & Neonatal Medicine, 26, 66-70, 2013 **Ref Id** 658483 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** evaluate urine PCR alone and with uric acid and clinical factors to predict or exclude significant proteinuria (>300mg/day) in PE evaluations **Study dates** 2005 - 2007 **Source of funding** Not reported	**Characteristics** <u>women with proteinuria≥300mg/day</u> age: 27.5 SD 6.7 years (range 26.4-28.6) GA at study: 31.3 SD 3.8 weeks (range 30.7-31.9) SBP at first visit: 120.9 SD 18.4 mmHg (115.2-126.7) SBP (mean at study time): 147.5 SD 13.0 mmHg (145.3-149.6) DBP at first visit: 71.3 SD 16.5 mmHg (66.2-76.5) DBP (mean at study time): 89.4 SD 10.9 mmHg (87.6-91.2) **Inclusion Criteria** all patients (GA≥20weeks) with signs or symptoms concerning for the diagnosis of PE who were seen in the obstetrical triage unit and underwent blood pressure monitoring and laboratory evaluation	Reference test: 24 hour urine collection	(benzenethonium chloride) technique for 24hr urine protein and random urine protein and enzymatic creatinase for random urine creatinine.	**>0.08: sens 97%; spec 15%; LR+ 1.14; LR- 0.23; [TP140; FP 180; FN 4; TN 32; back calculated by NGA]** >0.12: 90%; 39%; 1.48; 0.25; [TP 130; FP 129; FN14; TN 83; back calculated by NGA] **>0.19: 78%; 70%; 2.60; 0.31; [TP 112; FP 64; FN 32; TN 148; back calculated by NGA]** >0.40: 50%; 92%; 7.08; 0.53; [TP 72; FP 17; FN 72; TN 195; back calculated by NGA] >0.45: 47%; 96%; 11.0; 0.56; [TP 68; FP 8; FN 76; TN 204; back calculated by NGA] **>1.19: 31%; >99%; 33.1; 0.70; [TP 45; FP 2; FN 99; TN 210; back calculated by NGA]**	**using QUADAS-II <u>DOMAIN 1: PATIENT SELECTION</u> A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	Exclusion Criteria Proteinuria≥300mg/24hr before 20 weeks GA				**bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard ? unclear 2. If a threshold was used, was it pre-specified ? unclear **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **DOMAIN 4: FLOW AND TIMING** **A. RISK OF BIAS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					1. Was there appropriate interval between index tests and reference standard ? yes 2. Did all patients receive a reference standard ? yes 3. Did patients receive the same reference standard ? Yes 4. Were all patients included in the analysis? yes **Could the patient flow**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					have introduced bias? RISK: LOW **Other information**
Full citation Tun, C., Quinones, J. N., Kurt, A., Smulian, J. C., Rochon, M., Comparison of 12-hour urine protein and protein:creatinine ratio with 24-hour urine protein for the diagnosis of preeclampsia, American Journal of Obstetrics & Gynecology, 207, 233.e1-8, 2012 **Ref Id** 658513 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** evaluate the performance of the 12-hour urine protein >165 mg and PCR >0.15 for the prediction of 24 hour	**Sample size** n=102 enrolled; n=90 in final analysis (n=28 proteinuria≥300mg/24hrs) **Characteristics** women with proteinuria median age: 30 years (range 19-38) median GA: 32.8 weeks (range 24.0-35.4) median SBP on admission: 140 mmHg (117-158) median DBP on admission: 82 mmHg (64-112) **Inclusion Criteria** aged 18-55 years and GA>20 weeks admitted to the study antepartum unit who were undergoing a 24-hour urine collection for the	**Tests** Index test: urine PCR sample (initial urine specimen at time of presentation) - *if this was missed, it was taken from 24 hr collection itself, or immediately after 24hr collection* Reference test: 24 hr urine collection started on admission	**Methods** Only 24 hr urine collection was used for clinical management, spot PCR result unavailable to clinicians (blinded). Pre-specified PCR >0.15 to predict proteinuria≥300mg/24hrs for PE.	**Results** proteinuria≥300mg/24hrs n=28/90 pre-defined cut-off PCR 0.15 TN 30/62; TP 24/28; sens 89% (81-94); spec 49% (39-59); [FP 32; FN 4; back calculated by NGA]	**Limitations** **Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
urine protein of ≥300 mg in patients with suspected PE **Study dates** 1 July 2010 - 31 December 2011 **Source of funding** Lehigh Valley Health Network Department of Obstetrics and Gynecology Research Fund	diagnosis and/or management of PE **Exclusion Criteria** • known pre-pregnancy renal disease (defined as baseline 24hour urine protein≥300 mg) • clinical indication for delivery at the time of admission, • outside the maternal or gestational age parameters a • did not speak English • did not give informed consent for any reason • had been enrolled previously in the study				inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					results interpreted without knowledge of the results of the reference standard? yes 2. If a threshold was used, was it pre-specified? yes: 0.15 **Could the conduct or interpretation of the index test have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABIL**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					ITY Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **DOMAIN 3: REFERENCE STANDARD** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition ? yes 2. Were the reference standard results interpreted

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					without knowledge of the results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					DOMAIN 4: FLOW AND TIMING **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? Yes 4. Were all patients included in the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					analysis? No – included n=90/102; 88% (excluded n=11 for birth during 24hr collection; n=1 lab error) **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Valdes, E., Sepulveda-Martinez, A., Tong, A., Castro, M., Castro, D., Assessment of Protein: Creatinine Ratio versus 24-Hour Urine Protein in the Diagnosis of Preeclampsia, Gynecologic and Obstetric Investigation, 81, 78-83, 2016 **Ref Id**	**Sample size** n=72 in final analysis (proteinuria<300mg/day n=23/72; proteinuria>5g/day n=8/72) **Characteristics** age: 30.5 SD 5.95 years SBP: 151.6 SD 15.38 mmHg	**Tests** Index test: urine sample (15–20ml) collected for quantification of proteinuria and creatinuria concentrations Reference test: 24 hour urine collection (proteinuria>300mg/24hrs)	**Methods** Urine sample collected and stored at –20°C until end of study period (blinded to outcome)	**Results** proteinuria≥300mg/24hrs n=49/72 AUC: 0.8802 (95%CI 0.80230 - 0.95813) PCR cut-off: "optimal" at 0.36 sens 73%; spec 91% [TP 36; FP 2; FN 13; TN 21; back calculated by NGA]	**Limitations** **Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecut

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
838773 **Country/ies where the study was carried out** Chile **Study type** Prospective cohort study **Aim of the study** assess the effectiveness of the PCR in the differential diagnosis of pregnancy hypertensive disorder **Study dates** January 2012 - December 2012 **Source of funding** Oficina de Apoyo a la Investigación Clínica (OAIC) of Hospital Clínico Universidad de Chile (project No. 494/11; internal competition in free topics)	DBP: 94.3 SD 11.26 mmHg **Inclusion Criteria** Every woman admitted at the study hospital in study period with a diagnosis of pregnancy hypertensive disorder **Exclusion Criteria** • twin pregnancies • fetal birth defects (with antenatal diagnosis or diagnosed during the neonatal period) • chronic nephropathies • maternal age under 18 • gestational age <20 weeks • incomplete demographic and perinatal data				ive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard? unclear 2. If a threshold was used, was it pre-specified? no

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the referenc

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					e standard likely to correctly classify the target condition ? yes 2. Were the referenc e standard results interpret ed without knowled ge of the results of the index test? yes **Could the reference standard, its conduct, or its interpretatio n have introduced bias? RISK: LOW** **B. CONCERNS REGARDIN**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					G APPLICABILITY Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard ? yes 2. Did all patients receive a

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					2. Is the reference standard likely to correctly classify the target condition? yes 3. Did patients receive the same reference standard? Yes 4. Were all patients included in the analysis? yes **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Waugh, J., Hooper, R., Lamb, E., Robson, S., Shennan, A., Milne, F., Price, C., Thangaratinam, S., Berdunov, V., Bingham, J., Spot protein-creatinine ratio	**Sample size** n=1823 recruited; n=959 had all test data available (PE in n=475/959; severe PE in n=417/475)	**Tests** Index test: routine spot urine sample (recruitment sample): PCR and ACR (collected at recruitment, before 24 hr collection started)	**Methods** pre-specified thresholds of PCR≥30mg/mmol and ACR≥2mg/mmol. Proteinuria was defined as ≥300mg of protein from a 24 hour urine collection using the central laboratory's BZC assay.	**Results** **proteinuria≥300mg/24hrs n=475/959** ACR cut-off - *only data from **central laboratory ACR testing** of recruitment sample and central lab BZC assay of 24 hour urine (≥300mg/l) supplied*	**Limitations** **Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION**

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<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
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<td>and spot albumin-creatinine ratio in the assessment of pre-eclampsia: A diagnostic accuracy study with decision-analytic model-based economic evaluation and acceptability analysis, Health Technology Assessment, 21, 1-90, 2017

Ref Id

838777

Country/ies where the study was carried out

UK

Study type

Prospective cohort study

Aim of the study
evaluate the accuracy of quantitative assessments of spot PCR and spot ACR at different thresholds
in predicting severe PE compared with 24-hour urine protein measurement in pregnant women
with hypertension and suspected proteinuria

Study dates</td>
<td>Characteristics
median age: 30 years (IQR 26-34)
median GA: 37 weeks (IQR 36-39; range 23-43)
median SBP at recruitment: 145 mmHg (IQR 140-152)
median DBP at recruitment: 94 mmHg (IQR 90-100)

Inclusion Criteria
pregnant women aged ≥16 years, GA >20 weeks with new hypertension (systolic BP of ≥140 mmHg and/or diastolic BP of ≥90 mmHg) and a trace or more proteinuria on an automated dipstick urinalysis

Exclusion Criteria

• pre-existing renal disease (proteinuria before GA 20 weeks)</td>
<td>Reference test: 24 hour urine collection (proteinuria≥300mg/24hrs)</td>
<td>The start of 24-hour urine collection could be up to 24 hours after the random/recruitment sample test. A small amount of urine (five 1-ml aliquots) was taken from each
participant’s random/recruitment sample, frozen and stored at –80°C for secondary analysis. The remainder of
the random/recruitment sample was sent to the local laboratory for quantitative assessments of PCR.
Urine samples were sent from each participating site to a central laboratory for analysis using standardised methods. All data were entered into a clinical data management software package supplied by MedSciNet (Stockholm, Sweden)with web-based entry from each of the 36 clinical sites as well as the central lab:

• 24hr urine sample at central lab (BZC assay)
• ACR at central lab
• PCR at local laboratory
• PCR at central lab (BZC assay)
• PCR at central lab (PGR assay)</td>
<td>2mg/mmol (pre-specified): sens 99% (98 to 100); spec 23% (20 to 27; LR+ 1.29 (1.23 to 1.35); LR- 0.03 (0.00 to 0.07)
AUC: 0.92 (95%CI 0.91 to 0.94)
<table>
<tr><th></th><th>Ref +ve</th><th>Ref -ve</th><th>total</th></tr>
<tr><td>ACR≥2</td><td>471</td><td>359</td><td>830</td></tr>
<tr><td>ACR<2</td><td>4</td><td>125</td><td>129</td></tr>
<tr><td>total</td><td>475</td><td>484</td><td>959</td></tr>
</table>
PCR cut-off 30mg/mmol (pre-specified):
<u>data from local laboratory PCR testing of recruitment urine sample and central lab BZC assay of 24 hour urine (≥300mg/l)</u>
Sensitivity 93% (95%CI 90 to 95); Specificity 62% (95%CI 58 to 67); LR+ 2.47 (95%CI 2.18 to 2.76); LR- 0.11 (95%CI 0.08 to 0.15)
AUC: 0.90 (95%CI 0.88 to 0.92)
<table>
<tr><th></th><th>Ref +ve</th><th>Ref -ve</th><th>total</th></tr>
<tr><td>PCR≥30</td><td>441</td><td>182</td><td>623</td></tr>
<tr><td>PCR<30</td><td>34</td><td>302</td><td>336</td></tr>
<tr><td>total</td><td>475</td><td>484</td><td>959</td></tr>
</table>
</td>
<td>A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? yes
2. Was a case-control design avoided? yes
3. Did the study avoid inappropriate exclusions? yes

Could the selection of patients have introduced bias? RISK: LOW

B. CONCERNS REGARDIN</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>33 months up to 30 November 2015

Source of funding
National Institute Health Research (NIHR) Health Technology Assessment (HTA) programme as project number 10/65/02</td>
<td>• pre-gestational diabetes
• chronic hypertension</td>
<td></td>
<td></td>
<td><u>data from central laboratory PCR testing (BZC assay) of recruitment urine sample and central lab BZC assay of 24 hour urine (≥300mg/l)</u>
Sens 93% (90 to 95); spec 68% (63 to 72); LR+2.88 (2.50 to 3.26); LR- 0.11 (0.07 to 0.14)
AUC: 0.91 (95%CI 0.90 to 0.93)
<table>
<tr><td></td><td>Ref +ve</td><td>Ref - ve</td><td>total</td></tr>
<tr><td>PCR≥30</td><td>441</td><td>156</td><td>597</td></tr>
<tr><td>PCR<30</td><td>34</td><td>328</td><td>362</td></tr>
<tr><td>total</td><td>475</td><td>484</td><td>959</td></tr>
</table>
<u>data from central laboratory PCR testing (PGR assay) of recruitment urine sample and central lab BZC assay of 24 hour urine (≥300mg/l)</u>
Sens 95% (92 to 97); spec 56% (51 to 60); LR+ 2.14 (1.93 to 2.35); LR- 0.09 (0.00 to 0.07)
AUC: 0.91 (95%CI 0.89 to 0.93)
<table>
<tr><td></td><td>Ref +ve</td><td>Ref - ve</td><td>total</td></tr>
<tr><td>PCR≥30</td><td>451</td><td>184</td><td>635</td></tr>
<tr><td>PCR<30</td><td>24</td><td>300</td><td>324</td></tr>
</table>
</td>
<td>G APPLICABILITY Is there concern that the included patients do not match the review question? CONCERN: LOW

<u>DOMAIN 2: INDEX TESTS</u>
A. RISK OF BIAS

1. Were the index test results interpreted without knowledge of the results of the reference standard? yes
2. If a threshold was used,</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				total 475 484 959	was it pre-specified ? yes, but also tested for other thresholds **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR – different results for different testing sites/assays for PCR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition ? yes 2. Were the reference standard results interpreted without knowledge of the results of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. RISK OF BIAS 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? Yes 4. Were all patients included in the analysis? No – included

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					n=959/1823; 53% (165 refused consent; 212+476+10 missing lab test results; 1 missing perinatal outcome) **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Waugh, J. J. S., Bell, S. C., Kilby, M. D., Blackwell, C. N., Seed, P., Shennan, A. H., Halligan, A. W. F., Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: A study of diagnostic accuracy, BJOG: An International Journal of Obstetrics and	**Sample size** n=171 enrolled (n=77/171 proteinuria≥ 300mg/24hr; n=17/77 proteinuria≥ 1g/24hrs; n=6/17 proteinuria≥ 4g/24hrs) **Characteristics** age: 29 years (range 19-40)	**Tests** Index test: DCA2000 from random urine sample for ACR (early morning/first void sample - final sample of 24 hr collection) Reference test: 24 hour urine collection (proteinuria≥300mg/24hr); the first void was discarded and the sample started with the	**Methods** DCA 2000 (Bayer) is a 'point of care system' for the estimation of microalbumin/creatinine ratio (ACR) utilising a cartridge system and a 40µL sample of urine. 24-hour urine samples were analysed in the Chemical Pathology Department of the Leicester Royal Infirmary by benzethonium chloride assay (BCA).	**Results** **n=77/171 proteinuria≥300mg/24hr** Quantitative microalbumin (DCA 2000) **AUC: 0.82 (95%CI 0.88 to 0.97)** "optimal" cut-off: 2.0mg/mmol: Sens 94% (95%CI 85 to 98); spec 94% (95%CI 85 to 98); LR+ 14.6 (6.74 to 31.8); LR- 0.069 (0.030 to 0.16); [TP 72; FP 6; FN 5; TN 88; back calculated by NGA]	**Limitations Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecut

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Gynaecology, 112, 412-417, 2005 **Ref Id** 838779 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** compare semi-quantitative visual and automated methods of urine testing with fully quantitative point of care urinalysis (ACR) for the detection of significant proteinuria (300mg/24hrs) in pregnancy complicated by hypertension **Study dates** October 2000 - June 2001 **Source of funding** No funding reported. Authors acknowledge Bayer for supplying the urinanalysers and dipsticks	**Inclusion Criteria** GA>20weeks referred to day assessment unit for new hypertension (first time in pregnancy) **Exclusion Criteria** pre- existing hypertension	second urine specimen, final specimen was first void the following day	For dipstick tests (unclear if blinded for DCA test): The early morning/first void urine sample was first tested visually by two trained observers who were blinded to each other's results as well as to the results from the reference standard		ive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard ? unclear - mentions blinding for dipstick analysis, not DCA 2000 analysis

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					2. If a threshold was used, was it pre-specified ? no **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					DOMAIN 3: REFERENCE STANDARD **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					its interpretation have introduced bias? RISK: LOW **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? Yes 4. Were all patients included in the analysis? yes **Could the patient flow have introduced bias? RISK: LOW**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Other information
Full citation Wheeler, Thomas L., 2nd, Blackhurst, Dawn W., Dellinger, Eric H., Ramsey, Patrick S., Usage of spot urine protein to creatinine ratios in the evaluation of preeclampsia, American Journal of Obstetrics and Gynecology, 196, 465.e1-4, 2007 **Ref Id** 838781 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** compare spot urine PCRs with 24 hour urine collections for protein in women being evaluated for PE **Study dates** December 2000 - July 2002	**Sample size** n=154 recruited; n=126 in final analysis **Characteristics** age: 26.6 SD 5.8 years GA: 34.0 SD 3.3 weeks **Inclusion Criteria** Met inpatient admission criteria for the evaluation of PE: • new-onset persistent hypertension: SBP>140mmHg or DBP>90mmHg after 20wks GA (previously normotensive) • worsening hypertension: increase in BP from baseline taken before 2wks GA • proteinuria included patients with renal disease, chronic	**Tests** Index test: urine sample for PCR (beginning of 24hr urine collection. No first morning voids) Reference test: 24 hour urine collection (proteinuria≥300mg/24hrs)	**Methods** Urinary protein was determined by the Biuret method. Urinary creatinine was determined by the 2-point rate method, aliquots were analyzed by a Johnson & Johnson Vitros 250 (Johnson & Johnson Clinical Diagnostics Inc, Rochester, NY)	**Results** n=68/126 with proteinuria≥300mg/24hrs; n=9/68 missed (false neg rate) "optimal" cut-off (from AUC of 0.86): 0.21 Sens 86.8%; spec 77.6%; [TP 59; FP 13; FN 9; TN 45; back calculated by NGA]	**Limitations** **Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not reported	hypertension, and diabetes, in whom preexisting proteinuria could exist **Exclusion Criteria** Women who had bacteriuria on microscopy or were on more than 24 hours bed rest				exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpret

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					ed without knowledge of the results of the reference standard ? unclear 2. If a threshold was used, was it pre-specified ? no **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition ? yes 2. Were the reference standard results interpreted without knowled

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					ge of the results of the index test? unc lear **Could the reference standard, its conduct, or its interpretatio n have introduced bias? RISK: LOW** **B. CONCERNS REGARDIN G APPLICABIL ITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					DOMAIN 4: FLOW AND TIMING **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? Yes 4. Were all patients included in the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					analysis? No – included n=126/154; 82% (n=28 went into labour during 24 hour collection) **Could the patient flow have introduced bias? RISK: LOW** **Other information**
Full citation Wilkinson,C., Lappin,D., Vellinga,A., Heneghan,H.M., O'Hara,R., Monaghan,J., Spot urinary protein analysis for excluding significant proteinuria in pregnancy, Journal of Obstetrics and Gynaecology, 33, 24-27, 2013 **Ref Id** 273183	**Sample size** n=132 24hr urine collections/analyses (performed on 89 women) **Characteristics** No information for maternal age, BP, or GA	**Tests** Index tests: First and last void urine samples were analysed for PCR (PCR1, PCR2) and ACR (ACR1, ACR2) then added back into 24 hr collection Reference test: 24 hour urine collection	**Methods** PCR and ACR were calculated on 132 first and last void urine samples during 24hr collection (and added to collection) Roche Cobas 6000 (Roche Diagnostics GmbH, D68298, Mannheim) performed the protein, albumin and creatinine assays. Protein analysis was performed using the turbidimetric method. Albuminuria was	**Results** n=76/132 had proteinuria<300mg/24hrs (n=56 proteinuria≥300mg/24hrs) <u>PCR cut-offs: 30, 25, 20, 15, 10 mg/mmol</u> 30: Sensitivity 83.9% (95%CI 72.2-91.3); specificity 97.4% (95%CI 90.0-99.3); FN 9/83; [TP 47; FP 2; FN 9; TN 74; back calculated by NGA] 25: 86.2 (75.1-92.8); 91.9 (83.4-96.2); 8/74; [TP 48; FP 6; FN 8; TN 70; back calculated by NGA]	**Limitations** **Risk of bias assessed using QUADAS-II** **<u>DOMAIN 1: PATIENT SELECTION</u>** **A. RISK OF BIAS** 1. Was a consecutive or

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Ireland **Study type** Prospective cohort study **Aim of the study** compare the accuracy of urinary PCR and ACR in defining optimal cut-off points to rule-out significant proteinuria (≥300 mg/24hrs) in pregnancy **Study dates** July 2009 - May 2010 **Source of funding** Not reported	**Inclusion Criteria** GA>20weeks admitted for suspected PE **Exclusion Criteria** No exclusion criteria were applied		quantified using the immunoturbidimetric assay.	20: 96.4 (87.9-99.0); 84.2 (74.4-90.7); 2/66; [TP 54; FP 12; FN 2; TN 64; back calculated by NGA] 15: 98.2 (90.6-99.7); 65.8 (54.6-75.5); 1/51; [TP 55; FP 26; FN 1; TN 50; back calculated by NGA] 10: FN 0/20 [TP 56; FP 56; FN 0; TN 20; back calculated by NGA] <u>ACR cut-offs: 3.5, 3.0, 2.5, 2.0, 1.5, 1.0 mg/mmol</u> 3.5: sensitivity 91.1% (95%CI 80.7-96.1); specificity 80.3% (95%CI 70.0-87.7); FN 5/66; [TP 51; FP 15; FN 5; TN 61; back calculated by NGA] 3.0: 91.1 (80.7-96.1); 78.9 (68.5-86.6); 5/65; [TP 51; FP 16; FN 5; TN 60; back calculated by NGA] 2.5: 96.4 (87.9-99.0); 77.6 (67.1-85.5); 2/61; [TP 54; FP 17; FN 2; TN 59; back calculated by NGA] 2.0: 96.4 (87.9-99.0); 72.4 (61.4-81.2); 2/57; [TP 54; FP 21; FN 2; TN 55; back calculated by NGA] 1.5: 96.4 (87.9-99.0); 65.8 (54.6-75.5); 2/52; [TP 54; FP 26; FN 2; TN 50; back calculated by NGA] 1.0: 98.2 (90.6-99.7); 48.7 (37.8-59.7); 1/38; [TP 55; FP 39; FN 1; TN 37; back calculated by NGA]	random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					not match the review question? CONCERN: LOW - note that 89 women provided the 132 samples used for analysis **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard? unclear 2. If a threshold was used,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					was it pre-specified ? no **Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **DOMAIN 3: REFERENCE STANDARD**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. RISK OF BIAS 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					bias? RISK: LOW **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and referenc

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					e standard ? yes 2. Did all patients receive a referenc e standard ? yes 3. Did patients receive the same referenc e standard ? Yes 4. Were all patients included in the analysis? yes **Could the patient flow have introduced bias? RISK: LOW** **Other information**

Appendix E – Forest plots

Figure 1: Forest plot for ACR cut-off 2.0 mg/mmol

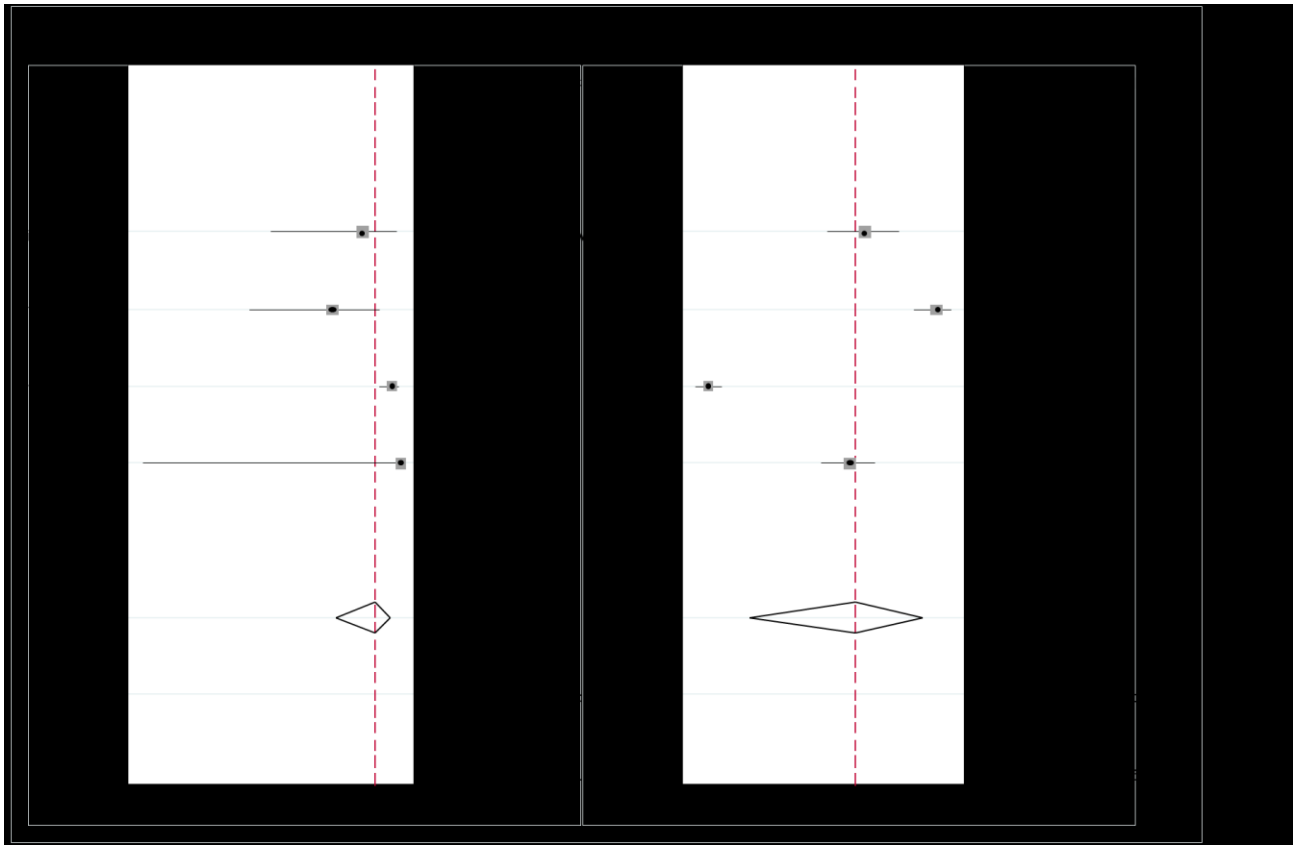


Figure 2: Forest plot for PCR cut-off 0.15 (15 mg/mmol)

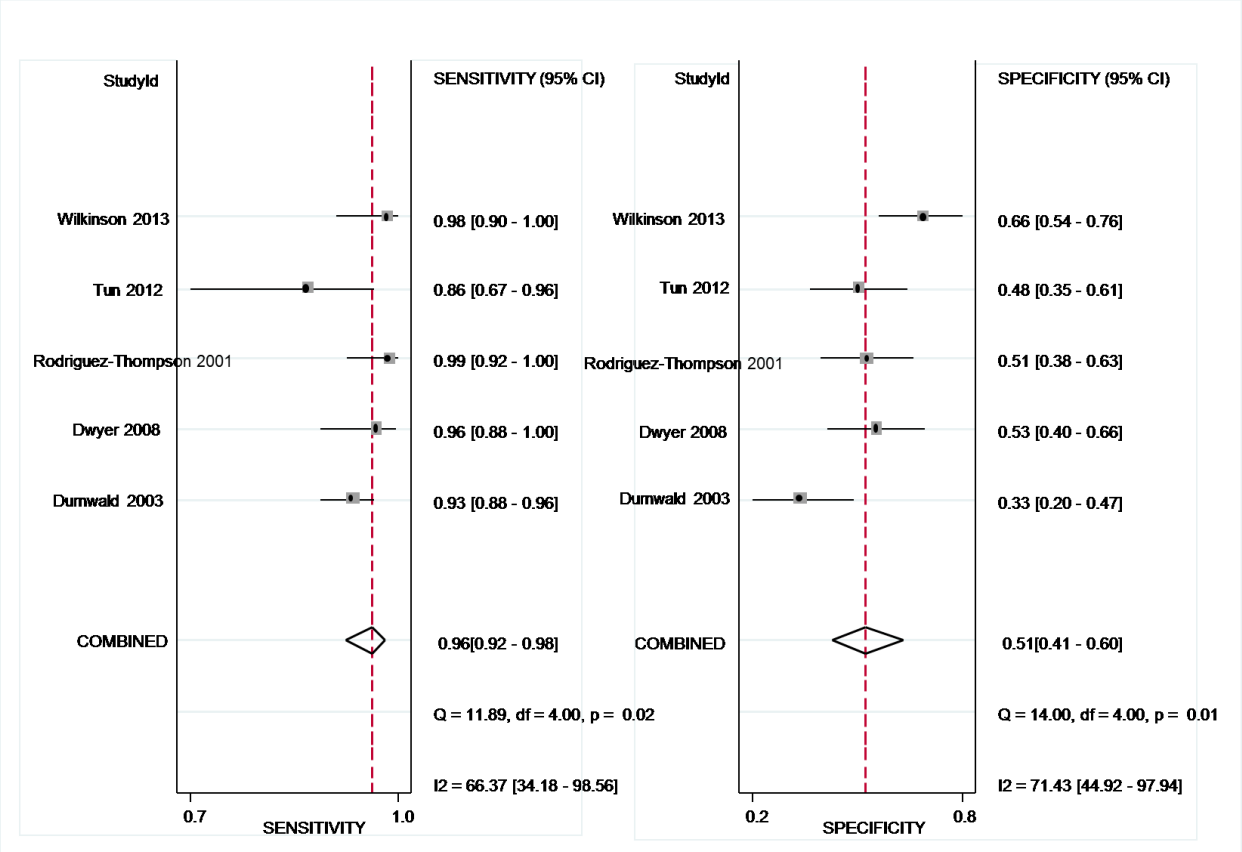


Figure 3: Forest plot for PCR cut-off 0.19 (19 mg/mmol)

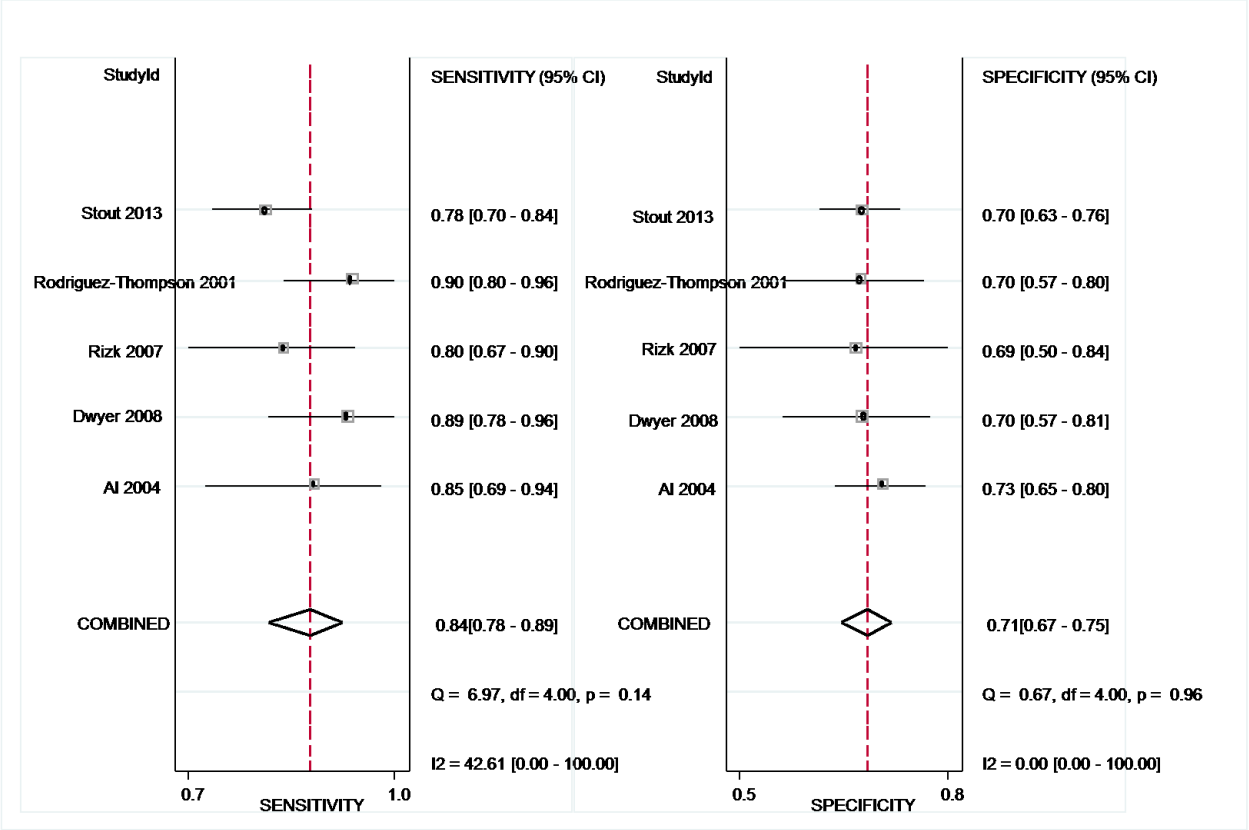


Figure 4: Forest plot for PCR cut-off 0.20 (20 mg/mmol)

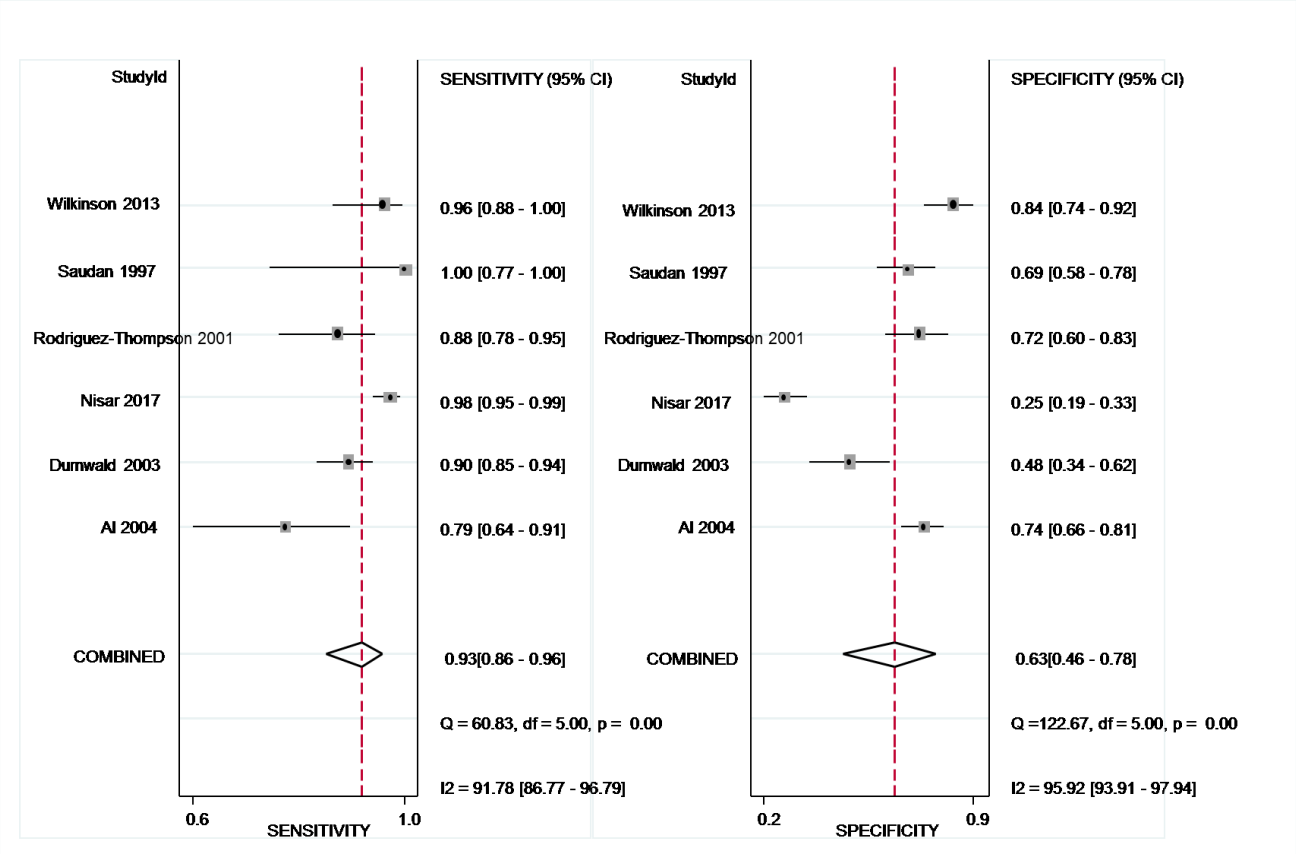


Figure 5: Forest plot for PCR cut-off 0.30 (30 mg/mmol): overall

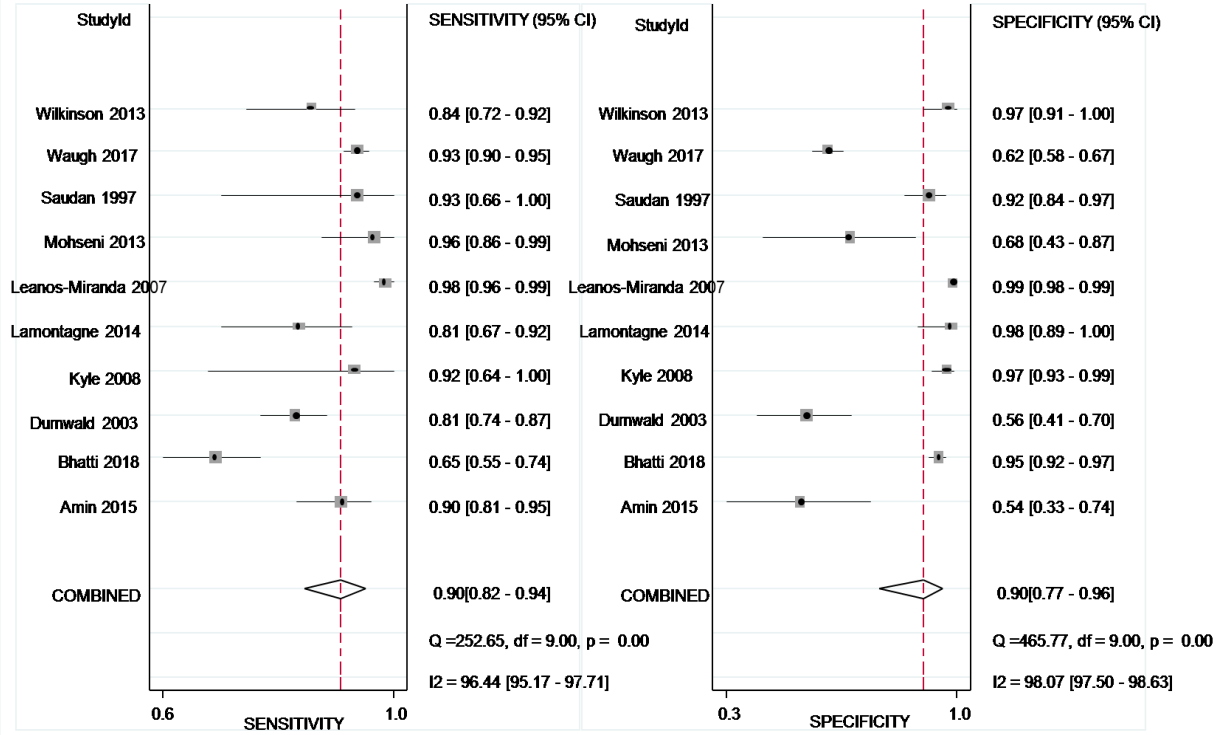


Figure 6: Forest plot for PCR cut-off 0.30 (30 mg/mmol): subgroup: studies that excluded first morning void for spot PCR sample

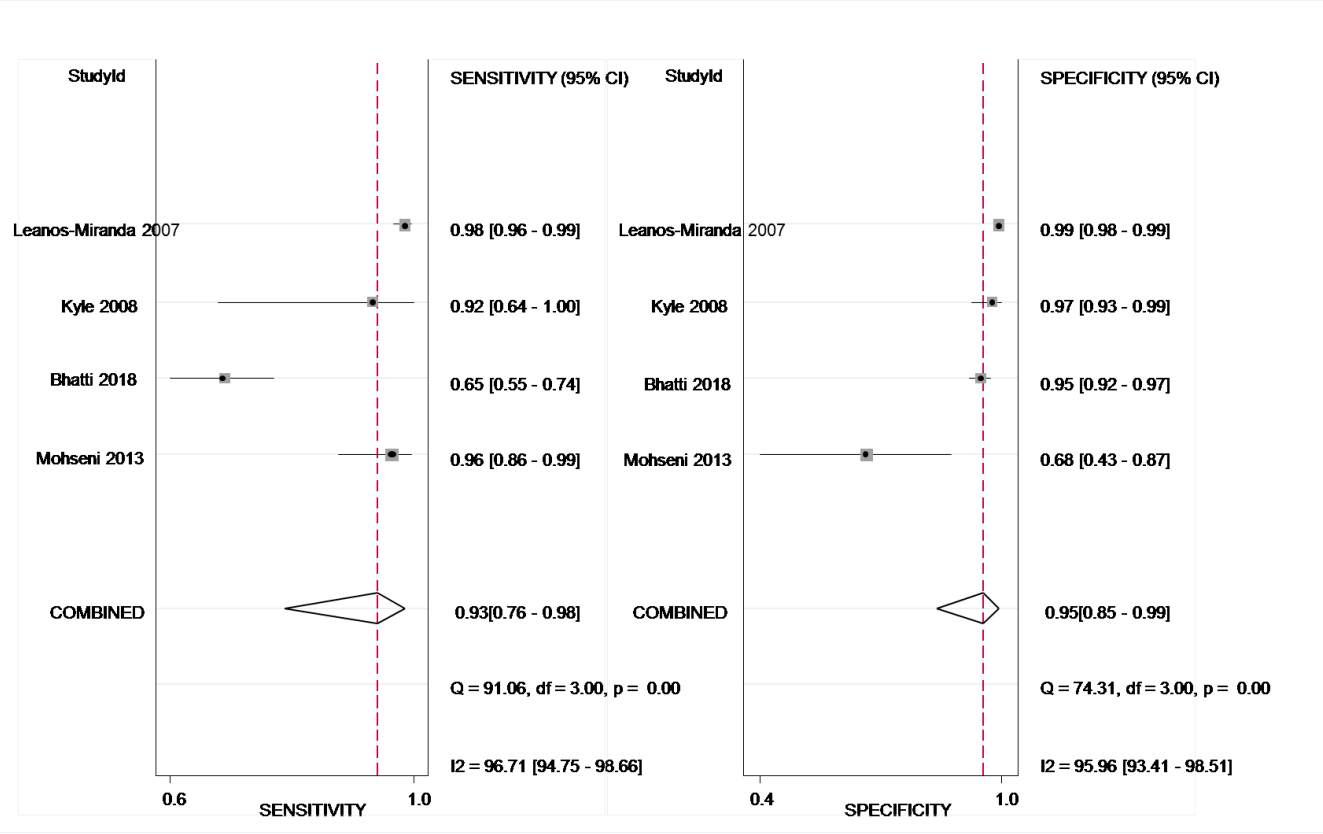


Figure 7: Forest plot for PCR cut-off 0.30 (30 mg/mmol): subgroup: studies that did not explicitly exclude first morning void, or stated it was included

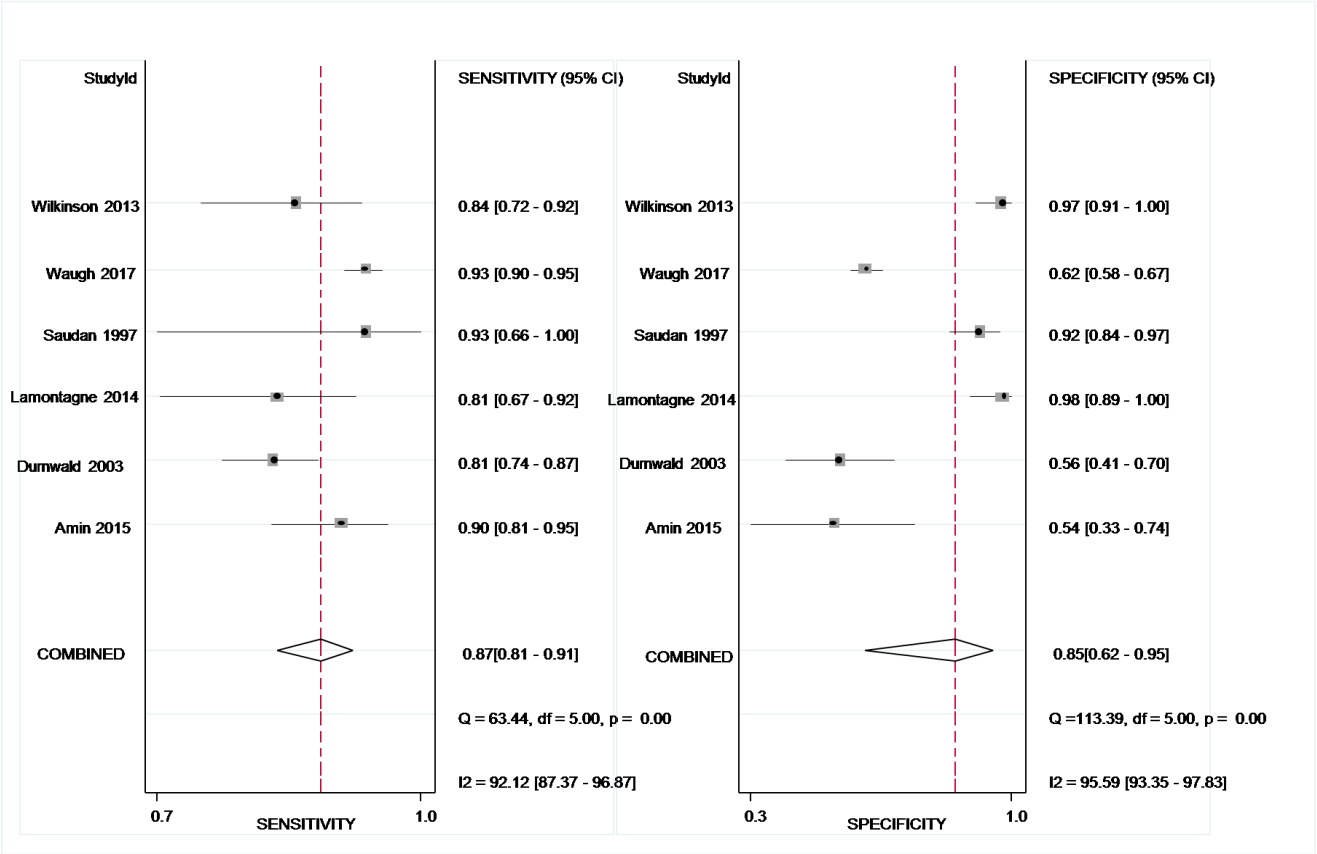


Figure 8: Forest plot for PCR cut-off 0.40 (40 mg/mmol)

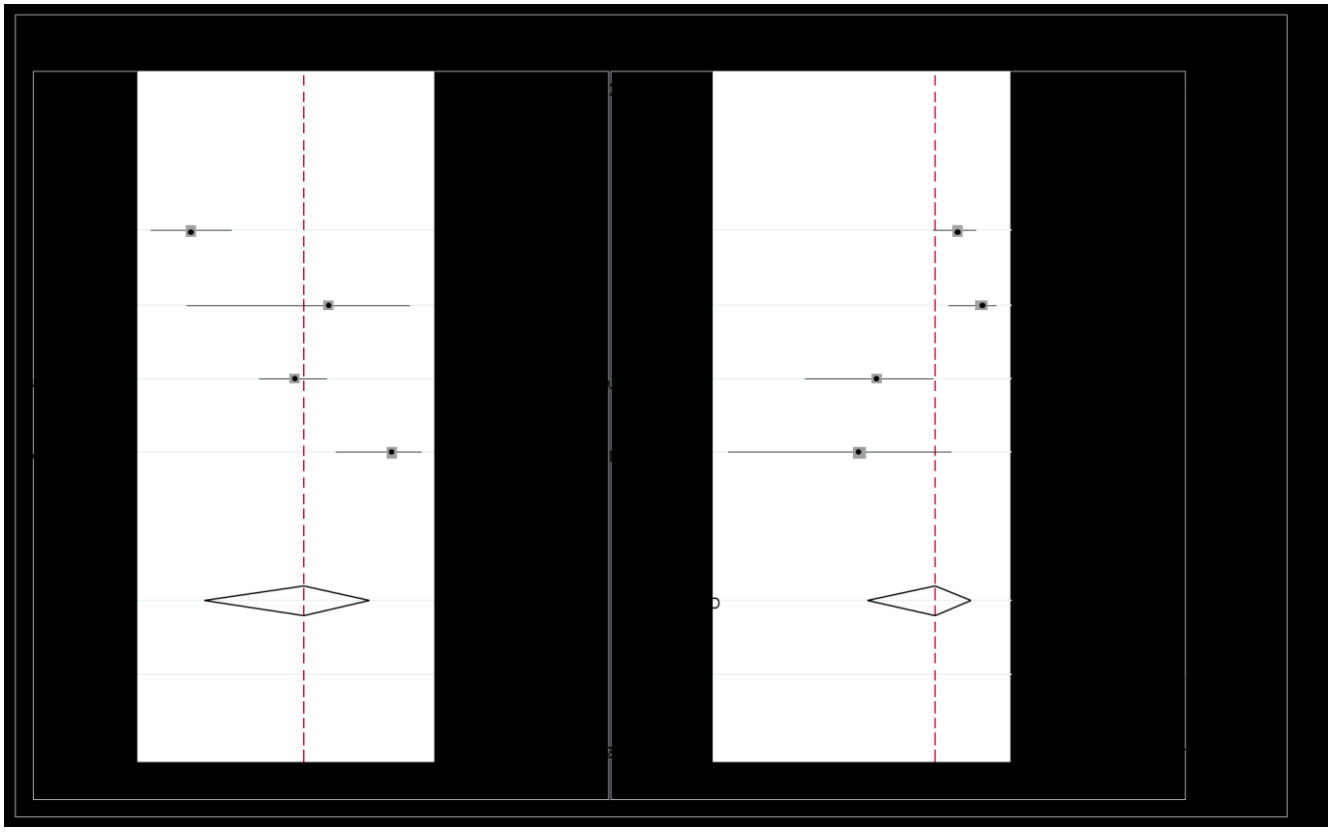
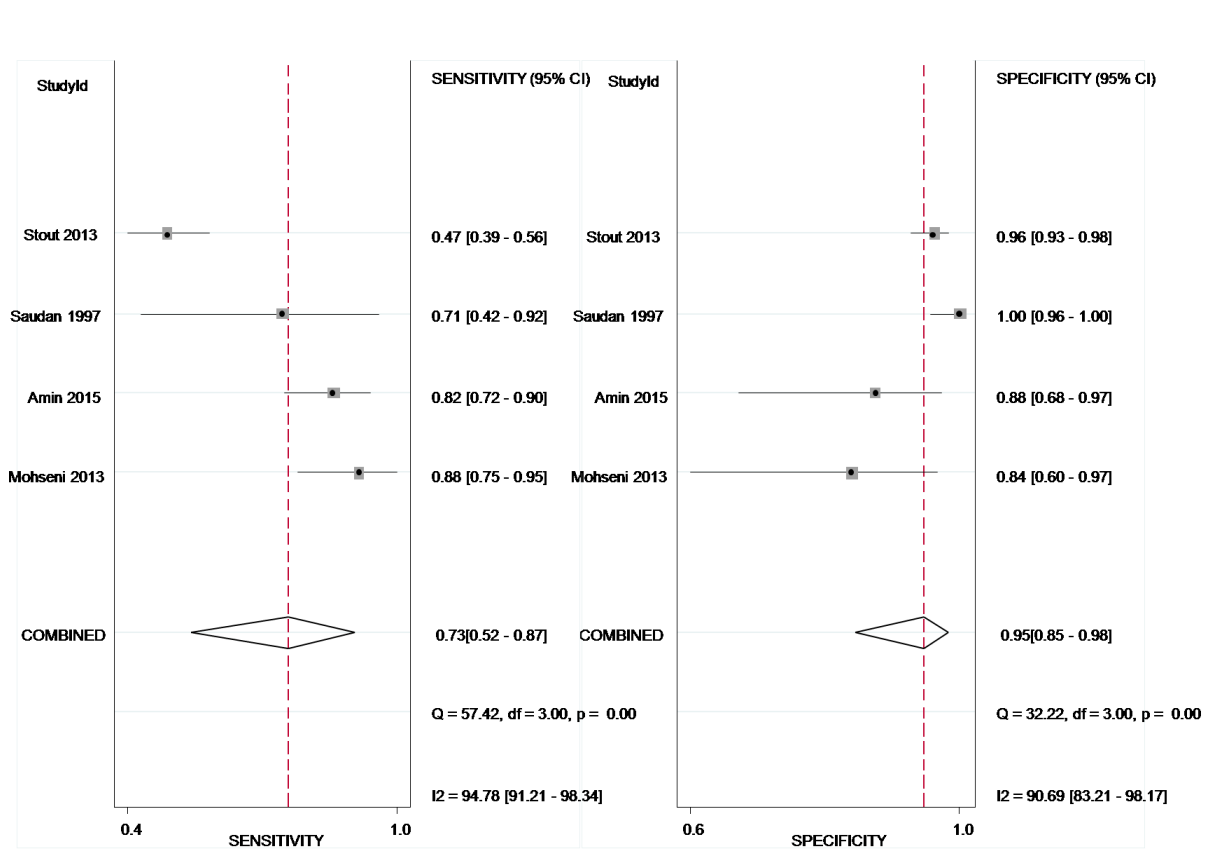


Figure 9: Forest plot for PCR cut-off 0.45 (45 mg/mmol)



Appendix F – GRADE tables

Table 5: Albumin:creatinine ratio (ACR) cut-off points for diagnosis of significant proteinuria (≥300mg/24hours) in pregnancy

ACR cut-point	Number of studies (author/s)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95%CI)	Effect size LR+ (95% CI) LR- (95% CI)	Quality of the evidence (GRADE)
1.0	1 (Wilkinson 2013)	N=132	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	0.98 (0.91 to 100.0)	0.49 (0.38 to 0.60)	-	1.91 (1.53 to 2.39)[2] 0.04 (0.01 to 0.26)[2]	MODERATE
1.5	1 (Wilkinson 2013)	N=132	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[3]	0.96 (0.88 to 0.99)	0.66 (0.55 to 0.76)	-	2.82 (2.06 to 3.87)[2] 0.05 (0.01 to 0.21)[2]	LOW
2.0	4 (Kyle 2008, Waugh 2005, Waugh 2017, Wilkinson 2013)	N=1412	No serious risk of bias	Very serious[4]	Serious[1]	No serious imprecision	0.98 (0.94 to 0.99)	0.69 (0.38 to 0.89)	0.97 (0.96 to 0.98)	3.18 (1.31 to 7.70) 0.04 (0.02 to 0.07)	VERY LOW
2.5	1 (Wilkinson 2013)	N=132	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[3]	0.96 (0.88 to 0.99)	0.78 (0.67 to 0.86)	-	4.31 (2.82 to 6.57)[2] 0.05 (0.01 to 0.18)[2]	LOW
3.0	1 (Wilkinson 2013)	N=132	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[3]	0.91 (0.81 to 0.96)	0.79 (0.67 to 0.86)	-	4.33 (2.78 to 6.74)[2] 0.11 (0.05 to 0.26)[2]	LOW
3.5	1 (Kyle 2008)	N=150	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	1.00 (0.75 to 1.00)	0.88 (0.81 to 0.93)	0.99 (0.97 to 1.00)	8.1 (5.2 to 12.6) 0.0 (-)	LOW
3.5	1 (Wilkinson 2013)	N=132	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[3]	0.91 (0.81 to 0.96)	0.80 (0.70 to 0.88)	-	4.61 (2.91 to 7.31)[2] 0.11 (0.05 to 0.26)[2]	LOW
8.0	1 (Kyle 2008)	N=150	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	1.00 (0.75 to 1.00)	0.96 (0.92 to 0.99)	0.99 (0.97 to 1.00)	27.4 (11.6 to 64.8) 0.0 (-)	LOW

ACR cut-points in mg/mmol
ACR: albumin;creatinine ratio; AUC: area under the curve; CI: confidence intervals; LR+: positive likelihood ratio; LR-: negative likelihood ratio; mg: milligrams; mmol: millimole; N: number of women; NGA: National Guideline Alliance;
1 Quality of the evidence was downgraded by 1 level for indirectness (132 samples came from only 89 women, Wilkinson 2013);
2 Additional data (LRs with CIs) calculated by the NGA technical team using http://vassarstats.net/clin1.html;
3 Quality of the evidence was downgraded by 1 level as 1 MID threshold is crossed for sensitivity (lower 0.75, upper 0.90);
4 Quality of the evidence was downgraded by 2 levels as I^2=96% for sensitivity (I^2>75%);
5 Quality of the evidence was downgraded by 2 levels as 2 MID thresholds are crossed for sensitivity (lower 0.75, upper 0.90)

Table 6: Protein:creatinine (PCR) cut-offs for diagnosis of significant proteinuria (≥300mg/24hours) in pregnancy

PCR cut-point (ratio)	Number of studies (author/s)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95%CI)	Effect size LR+ (95% CI) LR- (95% CI)	Quality of the evidence (GRADE)
0.08	1 (Stout 2013)	N=356	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.97 (0.93 to 0.99)[1]	0.15 (0.11 to 0.21)[1]	0.82	1.14 (1.08 to 1.22)[1] 0.23 (0.07 to 0.51)[1]	HIGH
0.10	1 (Wilkinson 2013)	N=132	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	1.00 (0.92 to 1.00)[3]	0.26 (0.17 to 0.38)[3]	-	1.36 (1.19 to 1.55)[3] Not calculable[3]	MODERATE
0.12	1 (Stout 2013)	N=356	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.90 (0.84 to 0.94)[1]	0.39 (0.33 to 0.46)[1]	0.82	1.48 (1.32 to 1.67)[1] 0.25 (0.15 to 0.41)[1]	MODERATE
0.13	1 (Al 2004)	N=185	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.90 (0.76 to 0.97)	0.65 (0.57 to 0.73)	0.86 (0.80 to 0.93)	2.57 (2.01 to 3.28)[3] 0.16 (0.06 to 0.40)[3]	MODERATE
0.14	1 (Rodriguez-Thompson 2001)	N=138	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	1.00 (0.93 to 1.00)[1]	0.51 (0.39 to 0.63)[1]	0.91 (0.87 to 0.96)	2.03 (1.60 to 2.58)[3] Not calculable[3]	HIGH
0.15	5 (Durnwald 2003, Dwyer 2008, Rodriguez-Thompson 2001, Tun 2012, Wilkinson 2013)	N=696	No serious risk of bias	Serious[5]	Serious[2]	No serious imprecision	0.96 (0.92 to 0.98)	0.50 (0.41 to 0.60)	0.87 (0.83 to 0.89)	1.91 (1.57 to 2.39) 0.08 (0.04 to 0.18)	LOW
0.16	1 (Rodriguez-Thompson 2001)	N=138	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.99 (0.91 to 1.00)[1]	0.62 (0.50 to 0.73)[1]	0.91 (0.87 to 0.96)	2.62 (1.93 to 3.55)[3] 0.02 (0.00 to 0.17)[3]	HIGH
0.17	1 (Rodriguez-Thompson	N=138	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.94 (0.85 to 0.98)[1]	0.64 (0.51 to 0.75)[1]	0.91 (0.87 to 0.96)	2.60 (1.89 to 3.57)[3]	MODERATE

PCR cut-point (ratio)	Number of studies (author/s)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95%CI)	Effect size LR+ (95% CI) LR- (95% CI)	Quality of the evidence (GRADE)
	2001)									0.09 (0.03 to 0.24)[3]	
0.18	1 (Al 2004)	N=185	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	0.85 (0.70 to 0.94)	0.71 (0.63 to 0.78)	0.86 (0.80 to 0.93)	2.94 (2.20 to 3.92)[3] 0.22 (0.10 to 0.45)[3]	LOW
0.18	1 (Rodriguez-Thompson 2001)	N=138	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.90 (0.79 to 0.95)[1]	0.65 (0.53 to 0.76)[1]	0.91 (0.87 to 0.96)	2.58 (1.85 to 3.60) [3] 0.16 (0.08 to 0.32)[3]	MODERATE
0.19	5 (Al 2004, Dwyer 2008, Rizk 2007, Rodriguez-Thompson 2001, Stout 2013)	N=878	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.84 (0.78 to 0.89)	0.71 (0.67 to 0.75)	0.75 (0.71 to 0.78)	2.88 (2.46 to 3.36) 0.23 (0.16 to 0.32)	MODERATE
0.20	6 (Al 2004, Durnwald 2003, Nisar 2017, Rodriguez-Thompson 2001, Saudan 2997, Wilkinson 2013)	N=1179	No serious risk of bias	Very serious[7]	Serious[2]	Serious[4]	0.93 (0.86 to 0.96)	0.63 (0.46 to 0.78)	0.91 (0.88 to 0.93)	2.52 (1.63 to 3.91) 0.12 (0.06 to 0.21)	VERY LOW
0.21	1 (Bhatti 2018)	N=476	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.88 (0.80 to 0.93)	0.83 (0.79 to 0.87)	-	5.15 (4.07 to 6.52)[3] 0.15 (0.09 to 0.25)[3]	MODERATE
0.21	1 (Rodriguez-Thompson 2001)	N=138	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.88 (0.78 to 0.95)[1]	0.75 (0.63 to 0.85)[1]	0.91 (0.87 to 0.96)	3.59 (2.35 to 5.47)[3] 0.15 (0.08 to 0.30)[3]	MODERATE
0.21	1 (Wheeler 2007)	N=126	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.87 (0.76 to 0.93)[1]	0.78 (0.64 to 0.87)[1]	0.86	3.87 (2.38 to 6.30)[3]	MODERATE

PCR cut-point (ratio)	Number of studies (author/s)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95%CI)	Effect size LR+ (95% CI) LR- (95% CI)	Quality of the evidence (GRADE)
										0.17 (0.09 to 0.32)[3]	
0.22	1 (Eslamian 2011)	N=100	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	0.88 (0.73 to 0.95)[1]	0.93 (0.81 to 0.98)[1]	0.93 (0.85 to 1.00)	11.74 (4.54 to 30.34)[3] 0.14 (0.07 to 0.30)[3]	LOW
0.25	1 (Saudan 1997)	N=100	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	0.95 (0.64 to 1.00)[1]	0.84 (0.74 to 0.90)[1]	-	5.70 (3.46 to 9.41)[3] 0.09 (0.01 to 0.57)[3]	LOW
0.25	1 (Wilkinson 2013)	N=132	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[4]	0.86 (0.75 to 0.93)	0.92 (0.83 to 0.96)	-	10.86 (5.00 to 23.57)[3] 0.16 (0.08 to 0.30)[3]	LOW
0.28	1 (Dwyer 2008)	N=116	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.66 (0.52 to 0.78)	0.95 (0.86 to 0.99)	0.89 (0.83 to 0.95)	13.21 (4.32 to 40.45)[3] 0.36 (0.25 to 0.52)[3]	MODERATE
0.28	1 (Kucukgoz-Gulec 2017)	N=205	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.82 (0.75 to 0.87)[1]	0.71 (0.54 to 0.83)[1]	0.78	2.79 (1.73 to 4.52)[3] 0.26 (0.18 to 0.36)[3]	HIGH
0.30	10 (Amin 2015, Bhatti 2018, Durnwald 2003, Kyle 2008, Lamontagne 2014, Leanos-Miranda 2007, Mohseni 2013, Saudan 1997, Waugh 2017, Wilkinson 2013)	N=3224	No serious risk of bias	Very serious[7]	Serious[2]	Serious[4]	0.90 (0.82 to 0.94)	0.90 (0.77 to 0.96)	0.95 (0.93 to 0.97)	9.46 (3.72 to 24.05) 0.11 (0.06 to 0.20)	VERY LOW

PCR cut-point (ratio)	Number of studies (author/s)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95%CI)	Effect size LR+ (95% CI) LR- (95% CI)	Quality of the evidence (GRADE)
0.30 (subgroup – excluded 1st morning void)	4 (Bhatti 2018, Kyle 2008, Leanos-Miranda 2007, Mohseni 2013)	N=1620	No serious risk of bias	Very serious[7]	No serious indirectness	Serious[4]	0.93 (0.76 to 0.98)	0.95 (0.85 to 0.99)	0.98 (0.97 to 0.99)	19.19 (5.59 to 65.87) 0.07 (0.02 to 0.28)	VERY LOW
0.30 (subgroup – included or unclear whether used 1st morning void)	6 (Amin 2015, Durnwald 2003, Lamontagne 2014, Saudan 1997, Waugh 2017, Wilkinson 2013)	N=1604	No serious risk of bias	Very serious[7]	Serious[2]	Serious[4]	0.87 (0.81 to 0.91)	0.85 (0.62 to 0.95)	0.91 (0.88 to 0.93)	5.87 (2.02 to 17.04) 0.15 (0.10 to 0.22)	VERY LOW
0.35	1 (Mohseni 2013)	N=67	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.94 (0.82 to 0.98)[3]	0.74 (0.49 to 0.90)[3]	0.89 (SE 0.06)	3.56 (1.67 to 7.59)[3] 0.08 (0.03 to 0.26)[3]	MODERATE
0.35	1 (Saudan 1997)	N=100	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	0.83 (0.56 to 0.97)[1]	0.95 (0.86 to 0.98)[1]	-	16.29 (6.13 to 43.29)[3] 0.15 (0.04 to 0.54)[3]	LOW
0.36	1 (Rizk 2007)	N=83	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.69 (0.54 to 0.80)[1]	0.78 (0.60 to 0.90)[1]	0.82 (0.72 to 0.91)	3.14 (1.59 to 6.20)[1] 0.40 (0.36 to 0.61)[8]	MODERATE
0.36	1 (Valdes 2016)	N=72	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.73 (0.59 to 0.85)[1]	0.91 (0.70 to 0.98)[1]	0.88 (0.80 to 0.96)	8.45 (2.22 to 32.10)[3] 0.29 (0.18 to 0.47)[3]	MODERATE
0.39	1 (Durnwald 2003)	N=220	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.73 (0.65 to 0.79)[1]	0.73 (0.59 to 0.84)[1]	0.80	2.70 (1.71 to 4.26)[3]	MODERATE

PCR cut-point (ratio)	Number of studies (author/s)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95%CI)	Effect size LR+ (95% CI) LR- (95% CI)	Quality of the evidence (GRADE)
										0.37 (0.29 to 0.49)[3]	
0.40	4 (Durnwald 2013, Mohseni 2013, Saudan 1997, Stout 2013)	N=743	No serious risk of bias	Very serious[7]	No serious indirectness	Serious[4]	0.73 (0.53 to 0.87)	0.88 (0.75 to 0.95)	0.89 (0.86 to 0.91)	6.01 (2.99 to 12.09) 0.30 (0.16 to 0.57)	VERY LOW
0.45	4 (Amin 2015, Mohseni 2013, Saudan 1997, Stout 2013)	N=625	No serious risk of bias	Very serious[7]	No serious indirectness	Serious[4]	0.73 (0.52 to 0.87)	0.95 (0.85 to 0.98)	0.93 (0.90 to 0.95)	13.71 (4.94 to 38.03) 0.29 (0.16 to 0.54)	VERY LOW
0.49	1 (Al 2004)	N=185	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.74 (0.58 to 0.87)	0.84 (0.77 to 0.90)	0.86 (0.80 to 0.93)	4.72 (3.11 to 7.17)[3] 0.30 (0.18 to 0.52)[3]	MODERATE
0.50	1 (Mohseni 2013)	N=67	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	0.88 (0.74 to 0.95)[3]	0.84 (0.60 to 0.96)[3]	0.89 (SE 0.06)	5.54 (1.95 to 15.74)[3] 0.15 (0.07 to 0.32)[3]	LOW
0.50	1 (Durnwald 2003)	N=220	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.63 (0.55 to 0.70)[1]	0.83 (0.69 to 0.91)[1]	0.80	3.65 (1.99 to 6.68)[3] 0.45 (0.36 to 0.55)[3]	HIGH
0.53	1 (Kucukgoz-Gulec 2017)	N=205	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.81 (0.74 to 0.85)[1]	0.93 (0.79 to 0.98)[1]	0.91	11.08 (3.72 to 33.03)[3] 0.20 (0.15 to 0.28)[3]	MODERATE
0.55	1 (Mohseni 2013)	N=67	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	0.83 (0.69 to 0.92)[3]	0.84 (0.60 to 0.96)[3]	0.89 (SE 0.06)	5.28 (1.85 to 15.02)[3]	LOW

PCR cut-point (ratio)	Number of studies (author/s)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95%CI)	Effect size LR+ (95% CI) LR- (95% CI)	Quality of the evidence (GRADE)
										0.20 (0.10 to 0.38)[3]	
0.55	1 (Rizk 2007)	N=83	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.53 (0.39 to 0.67)[1]	0.88 (0.70 to 0.96)[1]	0.82 (0.72 to 0.91)	4.24 (1.63 to 11.00) 0.54 (0.40 to 0.73)[8]	HIGH
0.60 (0.595)	1 (Mohseni 2013)	N=66[9]	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.92 (0.80 to 0.97)[1]	0.95 (0.69 to 1.00)[1]	0.89 (SE 0.06)	15.61 (2.33 to 104.72)[3] 0.09 (0.03 to 0.22)[3]	MODERATE
0.60 (0.599)	1 (Mohseni 2013)	N=67	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	0.83 (0.69 to 0.92)[3]	0.84 (0.60 to 0.96)[3]	0.89 (SE 0.06)	45.28 (1.85 to 15.02)[3] 0.20 (0.10 to 0.38)[3]	LOW
0.60	1 (Amin 2015)	N=102	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.76 (0.64 to 0.84)[1]	0.88 (0.67 to 0.97)[1]	-	6.05 (2.08 to 17.57)[1] 0.28 (0.19 to 0.42)[1]	MODERATE
0.63	1 (Park 2013)	N=46	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	0.87 (0.72 to 0.94)[1]	1.00 (0.20 to 1.00)[1]	0.96 (0.90 to 1.00)	Not calculable[3] 0.14 (0.06 to 0.29)[3]	LOW
0.75	1 (Amin 2015)	N=102	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	0.68 (0.56 to 0.78)[1]	1.00 (0.83 to 1.00)[1]	-	Not calculable[10] 0.32 (0.23 to 0.44)[1]	MODERATE
0.86	1 (Rizk 2007)	N=83	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.43 (0.30 to 0.58)[1]	0.94 (0.78 to 0.99)[1]	0.82 (0.72 to 0.91)	6.90 (1.74 to 27.39)[1] 0.61 (0.48 to 0.77)[8]	HIGH

PCR cut-point (ratio)	Number of studies (author/s)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95%CI)	Effect size LR+ (95% CI) LR- (95% CI)	Quality of the evidence (GRADE)
0.90	1 (Amin 2015)	N=102	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.62 (0.50 to 0.72)[1]	1.00 (0.83 to 1.00)[1]	-	Not calculable[10] 0.38 (0.29 to 0.51)[1]	HIGH
1.19	1 (Stout 2013)	N=356	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.31 (0.24 to 0.40) [1]	0.99 (0.96 to 0.99)[1]	0.82	33.10 (8.16 to 134.39)[1] 0.70 (0.62 to 0.77) [1]	HIGH
1.40	1 (Rizk 2007)	N=83	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.35 (0.23 to 0.50) [1]	0.97 (0.82 to 1.00) [1]	0.82 (0.72 to 0.91)	11.29 (1.58 to 80.55) [1] 0.67 (0.54 to 0.82)[8]	HIGH

Data presented as reported by individual studies, with additional data calculated by the NGA technical team using Vasserstats online calculator (http://vassarstats.net/clin1.html); imprecision assessed using sensitivity (critical outcome)
AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N: number of women; NGA: National Guideline Alliance; PCR: protein:creatinine ratio; SE: standard error;
1 Additional data - confidence intervals (95%CIs) - calculated by NGA technical team
2 Quality of the evidence was downgraded by 1 level for indirectness (132 samples came from only 89 women, Wilkinson 2013)
3 Additional data - outcome result and 95%CIs - calculated by NGA technical team
4 Quality of the evidence was downgraded by 1 level for imprecision as the 95%CI for sensitivity crosses 1 boundary for MID (lower 0.75, upper 0.90)
5 Quality of the evidence was downgraded by 1 level for inconsistency as the i^2 value (heterogeneity) exceeds 50% (but less than 75%)
6 Quality of the evidence was downgraded by 2 levels for imprecision as the 95%CI for sensitivity crosses 2 boundaries for MID (lower 0.75, upper 0.90)
7 Quality of the evidence was downgraded by 2 levels for inconsistency as the I^2 value (heterogeneity) exceeds 75%
8 Information reported for LR- in Rizk 2007 does not match calculations and other data presented within the paper. Recalculated by NGA technical team
9 Article reports total of n=66 participants. 2x2 data back-calculated by NGA at this threshold, assuming 66 participants. However, other data tables within the article suggest total n=67
10 Information reported for LR+ in Amin 2015 does not match calculations and other data presented within the paper. Footnote within paper: "0.5 was added to empty cells to calculate ratios". Recalculated by NGA technical team

Appendix G – Economic evidence study selection

Appendix H – Economic evidence tables

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

No economic evidence was identified for this review question

Appendix J – Health economic analysis

No health economic analysis was conducted for this review question

Appendix K – Excluded studies

Clinical studies

Table 7: Clinical excluded studies with reasons for exclusion

Study	Reason for Exclusion
Abdul-Khalek, R., Warren, W., Zenenberg, R., Use of random protein to creatinine ratio as a diagnostic tool in preeclampsia, American Journal of Obstetrics and Gynecology, 204, S308, 2011	Conference abstract
Aggarwal, N., Suri, V., Soni, S., Chopra, V., Kohli, H. S., A prospective comparison of random urine protein-creatinine ratio vs 24-hour urine protein in women with preeclampsia, Medscape journal of medicine, 10, 98, 2008	Reference standard not described. "Significant proteinuria" used as reference standard, but no information as to what constitutes this.
Al, R. A., Borekci, B., Yapca, O., Keles, S., Kadanali, S., Albumin/creatinine ratio for prediction of 24-hour albumin excretion of > or =2 g in manifest preeclampsia, Clinical & Experimental Obstetrics & Gynecology, 36, 169-72, 2009	Reference standard not as defined by the protocol. Study assessed diagnostic accuracy of PCR to identify >2g albuminuria in a 24 hour period. All participants had >300mg protein in 24 hours.
Asghania, M., Mirblouk, F., Atrkar Roshan, Z., Moslehi, M., Diagnostic accuracy of 4-hour protein in preeclampsia in pregnant women which refered to Alzahra Hospital of Rasht city in 2009, Iranian Journal of Reproductive Medicine, 9, 36-37, 2011	Conference abstract
Aziz,A., Elshahawy,Y., Sany,D., Elmandooh,M., Quantification of proteinuria in mild preeclampsia with random albumin creatinine ratio, NDT Plus, 3, iii344-iii345, 2010	Reference standard of "significant proteinuria" but not described further.
Baba, Y., Ohkuchi, A., Usui, R., Takahashi, H., Matsubara, S., Urinary protein-to-creatinine ratio indicative of significant proteinuria in normotensive pregnant women, Journal of Obstetrics & Gynaecology Research, 42, 784-8, 2016	All participants were normotensive. Incorrect population.
Baba, Y., Yamada, T., Obata-Yasuoka, M., Yasuda, S., Ohno, Y., Kawabata, K., Minakawa, S., Hirai, C., Kusaka, H., Murabayashi, N., Inde, Y., Nagura, M., Hamada, H., Itakura, A., Ohkuchi, A., Maeda, M., Sagawa, N., Nakai, A., Kataoka, S., Fujimori, K., Kudo, Y., Ikeda, T., Minakami, H., Urinary protein-to-creatinine ratio in pregnant women after dipstick testing: prospective observational study, BMC Pregnancy & Childbirth, 15, 331, 2015	Study compares dipstick proteinuria to spot PCR. No 24 hour collection (reference standard) was conducted.
Basharat, A., Ayub, S., Usmani, A. T., Random urine protein to creatinine ratio as a diagnostic tool of significant proteinuria in pre-eclampsia,	Conference abstract

Study	Reason for Exclusion
BJOG: An International Journal of Obstetrics and Gynaecology, 119, 22, 2012	
Basharat, A., Navid, S., Jamil, M., Ayub, S., Usmani, A. T., Spot protein to creatinine ratio a good alternative to 24 hour urinary protein for diagnosis of preeclampsia, Rawal Medical Journal, 42, 64-67, 2017	Population: women with pre-eclampsia (BP<140/90 and >1+on dipstick)
Berks, D., Hoedjes, M., Visser, W., Franx, A., Steegers, E. A. P., Duvekot, H., Is the protein:creatinine ratio in a single spot urine sample accurate enough to replace the 24-hour urine protein collection in the post partum follow-up of preeclampsia?, Reproductive Sciences, 17, 237A, 2010	Conference abstract
Bhide, A., Rana, R., Dhavilkar, M., Amodio-Hernandez, M., Deshpande, D., Caric, V., The value of the urinary protein:creatinine ratio for the detection of significant proteinuria in women with suspected preeclampsia, Acta Obstetricia et Gynecologica Scandinavica, 94, 542-6, 2015	Population: women with PE (BP>140/90 and dipstick >=1+)
Brown, M. A., Buddle, M. L., Inadequacy of dipstick proteinuria in hypertensive pregnancy, Australian & New Zealand Journal of Obstetrics & Gynaecology, 35, 366-9, 1995	Index test: urinary dipstick (not spot test)
Cade, Thomas J., de Crespigny, Paul Champion, Nguyen, Tien, Cade, John R., Umstad, Mark P., Should the spot albumin-to-creatinine ratio replace the spot protein-to-creatinine ratio as the primary screening tool for proteinuria in pregnancy?, Pregnancy Hypertension, 5, 298-302, 2015	Does not compare to gold standard (ACR compared to PCR)
Cade, Thomas J., Gilbert, Stacey A., Polyakov, Alex, Hotchin, Anne, The accuracy of spot urinary protein-to-creatinine ratio in confirming proteinuria in pre-eclampsia, The Australian & New Zealand journal of obstetrics & gynaecology, 52, 179-82, 2012	Population: women with pre-eclampsia (hypertension in pregnancy after 20 weeks gestation with one other clinical feature as defined by current SOMANZ guidelines)
Calix, R. X., Rodrigue Jr, C. Z., Weyer, K. L., Dornelles, A., Longo, S. A., Protein-creatinine ratio for the diagnosis of preeclampsia: Same cutoff value for everyone?, Obstetrics and Gynecology, 125, 47S, 2015	Conference abstract
Chandrasekaran, N., Bhide, A., Diagnostic accuracy of spot protein creatinine ratio(PCR) in comparison to 24 hour urine protein, Archives of Disease in Childhood: Fetal and Neonatal Edition, 98, 2013	Conference abstract
Chen, B. A., Parviainen, K., Jeyabalan, A., Correlation of catheterized and clean catch urine protein/creatinine ratios in preeclampsia	Reference standard is not 24 hour urine collection (instead urine sample by catheter)

Study	Reason for Exclusion
evaluation, Obstetrics & Gynecology, 112, 606-10, 2008	
Cheung, H. C., Leung, K. Y., Choi, C. H., Diagnostic accuracy of spot urine protein-to-creatinine ratio for proteinuria and its association with adverse pregnancy outcomes in Chinese pregnant patients with pre-eclampsia, Hong Kong Medical Journal, 22, 249-55, 2016	Population: women with pre-eclampsia (inclusion criteria: "women with diagnosis of PE")
Combs,C.A., Wheeler,B.C., Kitzmiller,J.L., Urinary protein/creatinine ratio before and during pregnancy in women with diabetes mellitus, American Journal of Obstetrics and Gynecology, 165, 920-923, 1991	No relevant outcomes reported
Cote, A. M., Brown, M. A., Lam, E., von Dadelszen, P., Firoz, T., Liston, R. M., Magee, L. A., Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review, BMJ, 336, 1003-6, 2008	All included studies checked for inclusion, and additional references assessed
Demirci, O., Kumru, P., Arinkan, A., Ardic, C., Arisoy, R., Tozkir, E., Tandogan, B., Ayvaci, H., Tugrul, A. S., Spot protein/creatinine ratio in preeclampsia as an alternative for 24-hour urine protein, Balkan Medical Journal, 32, 51-5, 2015	Case-control study
Ethridge, J., Mercer, B., Can preeclampsia be preliminarily diagnosed or excluded when the urine protein:creatinine ratio (TPCR) is <300 mg/g?, American Journal of Obstetrics and Gynecology, 208, S267, 2013	Conference abstract
Evans, W., Lensmeyer, J. P., Kirby, R. S., Malnory, M. E., Broekhuizen, F. F., Two-hour urine collection for evaluating renal function correlates with 24-hour urine collection in pregnant patients, The Journal of maternal-fetal medicine, 9, 233-7, 2000	Not spot PCR. Compares 2hr to 24hr collection
Fatemeh, V., Sedigheh, A., Zohreh, Y., Faezeh, P., Pouran, M., Protein/creatinine ratio on random urine samples for prediction of proteinuria in preeclampsia, Clinical Biochemistry, 44, S235, 2011	Conference abstract
Gangaram, R., Moodley, J., Manogaran, N., Pregnancy outcomes in hypertensive disorders of pregnancy using the diagnostic accuracy of the 24 hour urinary protein and urinary microalbumin: Creatinine ratio, International Journal of Gynecology and Obstetrics, 107, S186, 2009	Conference abstract
Gangaram, R., Moodley, J., Naicker, M., Accuracy of the spot urinary microalbumin: Creatinine ratio and visual dipsticks in hypertensive pregnant women, International	Wrong index test: Examines different dipstick (visual and automatic) compared to 24hr urine collection

Study	Reason for Exclusion
Journal of Gynecology and Obstetrics, 107, S186-S187, 2009	
Gangaram, R., Naicker, M., Moodley, J., Comparison of pregnancy outcomes in women with hypertensive disorders of pregnancy using 24-hour urinary protein and urinary microalbumin to creatinine ratio, International Journal of Gynaecology & Obstetrics, 107, 19-22, 2009	Correlation of diagnostic accuracy with maternal and neonatal outcomes (same population as other Ganagaram 2009 paper - DTA data already assessed)
Garcia de Guadiana, L., Martinez, J., Gonzalez, M., Martin, E., Albaladejo, M. D., Lopez, R., Evaluation of spot urine protein-creatinine ratio to predict significant proteinuria during pregnancy, Clinical Chemistry and Laboratory Medicine, 49, S697, 2011	Conference abstract
Gaspari, Flavio, Perico, Norberto, Remuzzi, Giuseppe, Timed urine collections are not needed to measure urine protein excretion in clinical practice, American journal of kidney diseases : the official journal of the National Kidney Foundation, 47, 1-7, 2006	Narrative overview
Gonsales Valerio, Edimarlei, Lopes Ramos, Jose Geraldo, Martins-Costa, Sergio H., Muller, Ana Lucia Letti, Variation in the urinary protein/creatinine ratio at four different periods of the day in hypertensive pregnant women, Hypertension in Pregnancy, 24, 213-21, 2005	Reports correlation between PCR and 24hr urine. Unable to extract data for relevant outcomes
Haas, D. M., Sabi, F., McNamara, M., Rivera-Alsina, M., Comparing ambulatory spot urine protein/creatinine ratios and 24-h urine protein measurements in normal pregnancies, Journal of Maternal-Fetal & Neonatal Medicine, 14, 233-6, 2003	Development of a linear regression equation - no relevant outcomes
Haghighi, L., Nasiri, N., Ebrahimi, A., Najmi, Z., Moradi, Y., Hashemi, N., Predictive value of 4-, 8-, and 12-h urine protein and protein-to-creatinine ratio for detection of pre-eclampsia, International Journal of Gynaecology & Obstetrics, 134, 62-5, 2016	Not a relevant index test (uses 4h, 8h, 12h urine collection periods, not spot urine test)
Hatfield, T., Stephenson, M., Chung, J., Wing, D., Utilization of 4 and 8 hr urine collections compared to spot urine protein/creatinine (P/C) ratio and 24 hr urine protein collections for diagnosis of preeclampsia, American Journal of Obstetrics and Gynecology, 212, S128, 2015	Conference abstract
Hirshberg, A., Draper, J., Curley, C., Sammel, M. D., Schwartz, N., A random protein-creatinine ratio accurately predicts baseline proteinuria in early pregnancy, Journal of Maternal-Fetal & Neonatal Medicine, 27, 1834-8, 2014	Different reference standard: 150mg/24hrs, instead of 300mg/24hrs in early pregnancy (<20wks GA)

Study	Reason for Exclusion
Holbert, M., Tuemler, E., Namaky, D., The concordance of 24-hour urine total protein with protein/creatinine ratios in the diagnosis of preeclampsia, Obstetrics and Gynecology, 127, 154S-155S, 2016	Conference abstract
Hossain, N., Khan, N., Shah, N., Shah, T., Butt, S., Khanani, R., Spot urine protein-creatinine ratio and 24-h urine protein excretion: Diagnostic accuracy in women with pre-eclampsia, Pregnancy Hypertension, 4, 87-90, 2014	Population: women with pre-eclampsia (BP>140/90 and proteinuria >300mg/24hr)
Huang, Qitao, Gao, Yunfei, Yu, Yanhong, Wang, Wei, Wang, Shuoshi, Zhong, Mei, Urinary spot albumin:creatinine ratio for documenting proteinuria in women with preeclampsia, Reviews in obstetrics & gynecology, 5, 9-15, 2012	Population: women with PE (BP>140/90 after 20wks GA and dipstick test 1+; or chronic hypertension without proteinuria before the 20wks GA with new-onset dipstick test 1+)
Jaschevatzky, O. E., Rosenberg, R. P., Shalit, A., Zonder, H. B., Grunstein, S., Protein/creatinine ratio in random urine specimens for quantitation of proteinuria in preeclampsia, Obstetrics & Gynecology, 75, 604-6, 1990	Case control study: women with PE compared to healthy
Kasitanon, N., Chotayaporn, T., Wichainun, R., Sukitawut, W., Louthrenoo, W., Comparison of proteinuria determination by urine dipstick urine protein creatinine index (UPCI) and urine protein 24 hours in lupus patients, Lupus, 19, 58, 2010	Conference abstract
Kayatas, S., Erdogdu, E., Cakar, E., Yilmazer, V., Arinkan, S. A., Dayicioglu, V. E., Comparison of 24-hour urinary protein and protein-to-creatinine ratio in women with preeclampsia, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 170, 368-71, 2013	Cases with proteinuria <300mg/24hr were excluded from analysis
Khan, N., Hamilton, J., To what extent could greater use of laboratory quantification of proteinuria to distinguish between gestational hypertension and pre-eclampsia help to reduce caesarean section rate?, International Journal of Gynecology and Obstetrics, 119, S703, 2012	Conference abstract (poster)
Khashia, K. M., Willett, M. J., Elgawly, R. M., A 24-hour urine collection for proteinuria in pregnancy: Is it worthwhile doing the test?, Journal of Obstetrics and Gynaecology, 27, 388-389, 2007	Short communication. Unable to extract relevant data
Kumari, A., Singh, A., Singh, R., Evaluation of rapid diagnostic methods of urinary protein estimation in patients of preeclampsia of advanced gestational age, Journal of Obstetrics & Gynaecology of India, 63, 306-10, 2013	Population: women with pre-eclampsia (BP>140/90 and dipstick>1+or 200mg/24hr)
Lamb, E., Morosky, C. M., Optimal urine protein-to-creatinine ratio in the setting of co-existing	Conference abstract

Study	Reason for Exclusion
medical conditions, Obstetrics and Gynecology, 127, 74S, 2016	
Lopes Ramos, J. G., Martins-Costa, S. H., Mathias, M. M., Guerin, Y. L. S., Barros, E. G., Urinary protein/creatinine ratio in hypertensive pregnant women, Hypertension in Pregnancy, 18, 209-218, 1999	Unable to extract relevant data
Magee, L., Proteinuria in pregnancy, Pregnancy Hypertension, 1, S15, 2010	Conference abstract
Maldonado, A. E., Creatinine ratio and preeclampsia, Journal of Perinatal Medicine, 39, 2011	Conference abstract
Meyer, N. L., Mercer, B. M., Friedman, S. A., Sibai, B. M., Urinary dipstick protein: a poor predictor of absent or severe proteinuria, American Journal of Obstetrics & Gynecology, 170, 137-41, 1994	Index test: urinary dipstick (not spot test)
Mishra, V. V., Goyal, P. A., Priyankur, R., Choudhary, S., Aggarwal, R. S., Gandhi, K., Vyas, B., Hokabaj, S., Evaluation of Spot Urinary Albumin-Creatinine Ratio as Screening Tool in Prediction of Pre-eclampsia in Early Pregnancy, Journal of Obstetrics and Gynecology of India, 67, 405-408, 2017	Prediction of subsequent development of PE - not diagnostic. Did not compare to reference standard
Moiety, F. S., Mohamed, E. S. E. B., Attar, R. E., Kaffash, D. E., Albumin to creatinine ratio in a random urine sample: Correlation with severity of preeclampsia, Alexandria Journal of Medicine, 50, 139-142, 2014	Population: women with pre-eclampsia. Comparing mild PE and severe PE
Morris, R. K., Doug, M., Kilby, M. D., A systematic review and meta-analysis of the diagnostic accuracy of the spot Urinary protein creatinine ratio (PCR) and the spot urinary albumin creatinine ratio (ACR) in the management of suspected pre-eclampsia, Archives of Disease in Childhood: Fetal and Neonatal Edition, 96, 2011	Conference abstract. Full text publication identified
Morris, R. K., Riley, R. D., Doug, M., Deeks, J. J., Kilby, M. D., Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis, BMJ, 345, e4342, 2012	All included studies checked for inclusion, and additional references assessed
Neithardt, Adrienne B., Dooley, Sharon L., Borensztajn, Jayme, Prediction of 24-hour protein excretion in pregnancy with a single voided urine protein-to-creatinine ratio, American Journal of Obstetrics and Gynecology, 186, 883-6, 2002	Reports correlation between PCR and 24hr urine. No relevant outcomes

Study	Reason for Exclusion
Nipanal, H. V., Maurrya, D. K., Susmitha, S., Ravindra, P. N., Analysis of Proteinuria Estimation Methods in Hypertensive Disorders of Pregnancy, Journal of Obstetrics and Gynecology of India, 1-4, 2017	No confidence intervals reported. Unable to extract relevant data to calculate (reference standard results unavailable)
Nipanal, H. V., Maurya, D., Ananthanarayanan, P. H., Appropriate methods of urine protein estimation for predicting significant proteinuria in pregnancy complicated by hypertension, BJOG: An International Journal of Obstetrics and Gynaecology, 121, 97, 2014	Conference abstract
Nischintha, S., Pallavee, P., Ghose, Seetesh, Correlation between 24-h urine protein, spot urine protein/creatinine ratio, and serum uric acid and their association with fetomaternal outcomes in preeclamptic women, Journal of natural science, biology, and medicine, 5, 255-60, 2014	Population: women with pre-eclamspia (BP>140/90, on two occasions, or DBPâ‰¥110mmHg after 20wks GA, and proteinuria dipstick >=1+)
Nisell, H., Trygg, M., Back, R., Urine albumin/creatinine ratio for the assessment of albuminuria in pregnancy hypertension, Acta Obstetricia et Gynecologica Scandinavica, 85, 1327-1330, 2006	Population: women with pre-eclampsia (BP>140/90 and dipstick >1+)
Osmundson, S., Lafayette, R., Bowen, R., Roque, V., Aziz, N., Correlation of urine protein-creatinine ratios and 24-hour urinary excretion in twin pregnancies, American Journal of Obstetrics and Gynecology, 212, S124-S125, 2015	Conference abstract
Pahwa, M. B., Seth, S., Khosla, A., Significance of urine protein/creatinine ratio in pregnancy-induced hypertension, Clinica Chimica Acta, 382, 145-147, 2007	No relevant outcomes
Papanna, R., Mann, L. K., Kouides, R. W., Glantz, J. C., Protein/creatinine ratio in preeclampsia: a systematic review, Obstetrics & Gynecology, 112, 135-44, 2008	All included studies checked for inclusion, and additional references assessed
Payne, B., Magee, L. A., Cote, A. M., Hutcheon, J. A., Li, J., Kyle, P. M., Menzies, J. M., Peter Moore, M., Parker, C., Pullar, B., von Dadelszen, P., Walters, B. N., Douglas, M. J., Walley, K. R., Russell, J. A., Lee, S. K., Gruslin, A., Smith, G. N., Moutquin, J. M., Brown, M. A., Davis, G., Sass, N., Duan, T., Zhou, J., Mahajan, S., Noovao, A., McCowan, L. A., Moore, M. P., Bhutta, S. Z., Bhutta, Z. A., Hall, D. R., Steyn, D. W., Broughton Pipkin, F., Loughna, P., Robson, S., de Swiet, M., Walker, J. J., Grobman, W. A., Lindheimer, M. D., Roberts, J. M., Mark Ansermino, J., Benton, S., Cundiff, G., Hugo, D., Joseph, K. S., Lalji, S.,	PIERS study of women diagnosed with pre-eclampsia. No relevant outcomes. Study tested models to predict maternal and neonatal outcomes

Study	Reason for Exclusion
Lott, P., Ouellet, A. B., Shaw, D., Keith Still, D., Tawagi, G., Wagner, B., Biryabarema, C., Mirembe, F., Nakimuli, A., Tsigas, E., Merialdi, M., Widmer, M., PIERS Proteinuria: Relationship With Adverse Maternal and Perinatal Outcome, Journal of Obstetrics and Gynaecology Canada, 33, 588-597, 2011	
Price, C. P., Newall, R. G., Boyd, J. C., Use of protein: Creatinine ratio measurements on random urine samples for prediction of significant proteinuria: A systematic review, Clinical Chemistry, 51, 1577-1586, 2005	All included studies checked for inclusion, and additional references assessed
Rangasamy, S., Rao, A., Replacing 24-h albumin excretion with a shorter collection period in preeclampsia, Journal of Obstetrics and Gynecology of India, 62, 424-428, 2012	No relevant outcomes reported - correlation between PCR and 24hr collection, but no diagnostic accuracy
Riley, R. D., Ahmed, I., Ensor, J., Takwoingi, Y., Kirkham, A., Morris, R. K., Noordzij, J. P., Deeks, J. J., Meta-analysis of test accuracy studies: An exploratory method for investigating the impact of missing thresholds, Systematic Reviews, 4, 12, 2015	Methodology paper
Rimon, E., Shelf, M., Dovjic, S., Lessing, J. B., Kupferminc, M. J., The role of protein/creatinine ratio in random urine sample in the diagnosis of preeclampsia, Reproductive Sciences, 17, 127A-128A, 2010	Conference abstract
Risberg, A., Larsson, A., Olsson, K., Lyrenas, S., Sjoquist, M., Relationship between urinary albumin and albumin/creatinine ratio during normal pregnancy and pre-eclampsia, Scandinavian Journal of Clinical and Laboratory Investigation, 64, 17-23, 2004	No relevant outcomes - reported correlation of ACR and 24hr urine collection. Separated groups into normotensive and hypertensive
Robert, M., Sepandj, F., Liston, R. M., Dooley, K. C., Random protein-creatinine ratio for the quantitation of proteinuria in pregnancy, Obstetrics & Gynecology, 90, 893-5, 1997	No confidence interval reported, unable to extract data to calculate (reference standard results unavailable)
Rodrigue Jr, C. Z., Weyer, K. L., Dornelles, A., Longo, S. A., Comparison of timed urine collection to protein-creatinine ratio for the diagnosis of preeclampsia, Obstetrics and Gynecology, 123, 76S-77S, 2014	Conference abstract
Roudsari, F. Vahid, Ayati, S., Ayatollahi, H., Shakeri, M. T., Protein/creatinine ratio on random urine samples for prediction of proteinuria in preeclampsia, Hypertension in Pregnancy, 31, 240-2, 2012	No relevant outcomes - study reported correlation coefficient between PCR and 24hr urine
Sachan, Rekha, Patel, Munna Lal, Sachan, Pushpalata, Shyam, Radhey, Verma, Pratima, Dheeman, Soniya, Diagnostic accuracy of spot albumin creatinine ratio and its association with	No relevant outcomes - study compared ACR in normotensive, pre-eclampsia, and eclampsia

Study	Reason for Exclusion
fetomaternal outcome in preeclampsia and eclampsia, Nigerian medical journal : journal of the Nigeria Medical Association, 58, 58-62, 2017	
Saikul,S., Wiriyasirivaj,B., Charoenchinont,P., First 4-hour urinary protein - creatinine ratio for diagnosis of significant proteinuria in preeclampsia, Journal of the Medical Association of Thailand, 89 Suppl 4, S42-S46, 2006	Used 4-hr urine collection to compare to 24hr collection
Sanchez-Ramos, L., Gillen, G., Zamora, J., Stenyakina, A., Kaunitz, A. M., The protein-to-creatinine ratio for the prediction of significant proteinuria in patients at risk for preeclampsia: a meta-analysis, Annals of Clinical & Laboratory Science, 43, 211-20, 2013	All included studies checked for inclusion, and additional references assessed
Schubert, F. P., Abernathy, M. P., Alternate evaluations of proteinuria in the gravid hypertensive patient, Journal of Reproductive Medicine, 51, 709-14, 2006	Examines 12-hr collection compared to 24hr collection
Scifres, C., Stout, M., Stamilio, D., The diagnostic utility of urinary protein to creatinine ratio (UPC) for the detection of significant proteinuria, American Journal of Obstetrics and Gynecology, 204, S336, 2011	Conference abstract
Sethuram, R., Kiran, T. S. U., Weerakkody, A. N. A., Is the urine spot protein/creatinine ratio a valid diagnostic test for pre-eclampsia?, Journal of Obstetrics and Gynaecology, 31, 128-130, 2011	Population: women with pre-eclampsia (GA>24wks, BP>140/90 and dipstick >1+, or PE secondary to hypertension, gestational diabetes mellitus)
Sethuram, R., Kiran, T. U., Weerakkody, A., Spot protein creatinine ratio as the diagnostic test for pre-eclampsia: Why it is time to reconsider it?, BJOG: An International Journal of Obstetrics and Gynaecology, 116, 1412, 2009	Conference abstract
Shahbazian, N., Hosseini-Asl, F., A comparison of spot urine protein-creatinine ratio with 24-hour urine protein excretion in women with preeclampsia, Iranian journal of Kidney Diseases, 2, 127-31, 2008	No confidence intervals reported, and cannot be calculated from reported data (reference test results unavailable)
Shennan, A., Duhig, K., Random urine protein: Creatinine ratio was an accurate method for diagnosing proteinuria in pregnant women with hypertension, Evidence-Based Medicine, 13, 84, 2008	Abstract and editors commentary on Leanos-Miranda 2007 (assessed as full paper)
Sinno, O., Rood, K. M., Jones, M., Thung, S., Samuels, P., Buhimschi, I. A., Point-of-care vs laboratory based urine protein-creatinine ratio as an indicator of proteinuria in pregnancy, Obstetrics and Gynecology, 129, 145S, 2017	Conference abstract

Study	Reason for Exclusion
Skweres, Tomasz, Preis, Krzysztof, Ciepluch, Rafal, Miskiewicz, Krzysztof, [The value of a urine protein-to-creatinine ratio assessment in a single voided urine specimen in prediction of 24-hour proteinuria in pregnancy induced hypertension], Wartosc oznaczania wspolczynnika bialko/kreatynina w pojedynczej probce moczu w prognozie bialkomoczu dobowego u pacjentek z nadcisnieniem indukowanym ciaza., 77, 415-21, 2006	Article is in Polish
Taherian, A. A., Dehbashi, S., Baghban, M., The relationship between random urinary protein-to-creatinine ratio and 24-hours urine protein in diagnosis of proteinuria in mild preeclampsia, Journal of Research in Medical Sciences, 11, 6-12, 2006	Population: women with pre-eclampsia (dipstick>=1+and mild hypertension BP>=140/90)
Taheripanah, R., Kordlu, F., Hosseini, M., Protein/creatinine ratio in random urine as a rapid valuable criterion in diagnosis of pre-eclamsia in pregnant women, Iranian Journal of Reproductive Medicine, 8, 7-8, 2010	Conference abstract
Tun, C., Quinones, J., Kurt, A., Smulian, J., Rochon, M., Comparison of 12-hour urine and protein/creatinine ratio to 24-hour urine for the diagnosis of preeclampsia, American Journal of Obstetrics and Gynecology, 206, S331, 2012	Conference abstract
Verdonk, K., Hop, W. C. J., De Rijke, Y. B., Niemeijer, I. C., Steegers, E. A., Visser, W., Variation of urinary protein/creatinine ratio during the day in women suspected for preeclampsia, Pregnancy Hypertension, 2, 257, 2012	Conference abstract (poster)
Verdonk, K., Niemeijer, I. C., Hop, W. C. J., de Rijke, Y. B., Steegers, E. A. P., van den Meiracker, A. H., Visser, W., Variation of urinary protein to creatinine ratio during the day in women with suspected pre-eclampsia, BJOG : an international journal of obstetrics and gynaecology, 121, 1660-5, 2014	Population: Women with pre-eclampsia (GA>20wks, BP>=140/90 mmHg and dipstick >=1+; or chronic hypertension who developed new-onset proteinuria after mid-gestation)
Wikstrom,A.K., Wikstrom,J., Larsson,A., Olovsson,M., Random albumin/creatinine ratio for quantification of proteinuria in manifest pre-eclampsia, BJOG: An International Journal of Obstetrics and Gynaecology, 113, 930-934, 2006	Population: women with pre-eclampsia (significant protein in urine and hypertension)
Yamasmit, W., Chaithongwongwatthana, S., Charoenvidhya, D., Uerpairojkit, B., Tolosa, J. E., Random urinary protein-to-creatinine ratio for prediction of significant proteinuria in women with preeclampsia, Journal of Maternal-Fetal and Neonatal Medicine, 16, 275-279, 2004	Population: women with pre-eclampsia (GA>20wks, BP>=140/90 mmHg and dipstick >=1+; or chronic hypertension without proteinuria GA<20wks and new-onset urine protein dipstick >=1+(superimposed pre-eclampsia))

Study	Reason for Exclusion
Yamasmit, W., Charoenvidhya, D., Chaithongwongwatthana, S., Wongkitisophon, K., Uerpairojkit, B., Correlation between random urinary protein-to-creatinine ratio and quantitation of 24-hour proteinuria in preeclampsia, Journal of the Medical Association of Thailand, 86, 69-73, 2003	No relevant outcomes - study reports correlation coefficient between PCR and 24hr collection figuratively
Young, R. A., Buchanan, R. J., Kinch, R. A., Use of the protein/creatinine ratio of a single voided urine specimen in the evaluation of suspected pregnancy-induced hypertension, The Journal of family practice, 42, 385-9, 1996	Presents results using two cut-offs for each threshold (above and below, to rule in and rule out, leaving an "indeterminate" result between them). Relevant data could not be extracted. Available data is presented without CIs for AUC, sensitivity, and specificity
Zadehmodarres, S., Razzaghi, M. R., Habibi, G., Najmi, Z., Jam, H., Mosaffa, N., Kaboosi, M., Random urine protein to creatinine ratio as a diagnostic method of significant proteinuria in pre-eclampsia, Australian & New Zealand Journal of Obstetrics & Gynaecology, 46, 501-4, 2006	Case-control study (women with suspected PE and healthy controls)

Economic studies

Table 8: Economic excluded studies with reasons for exclusion

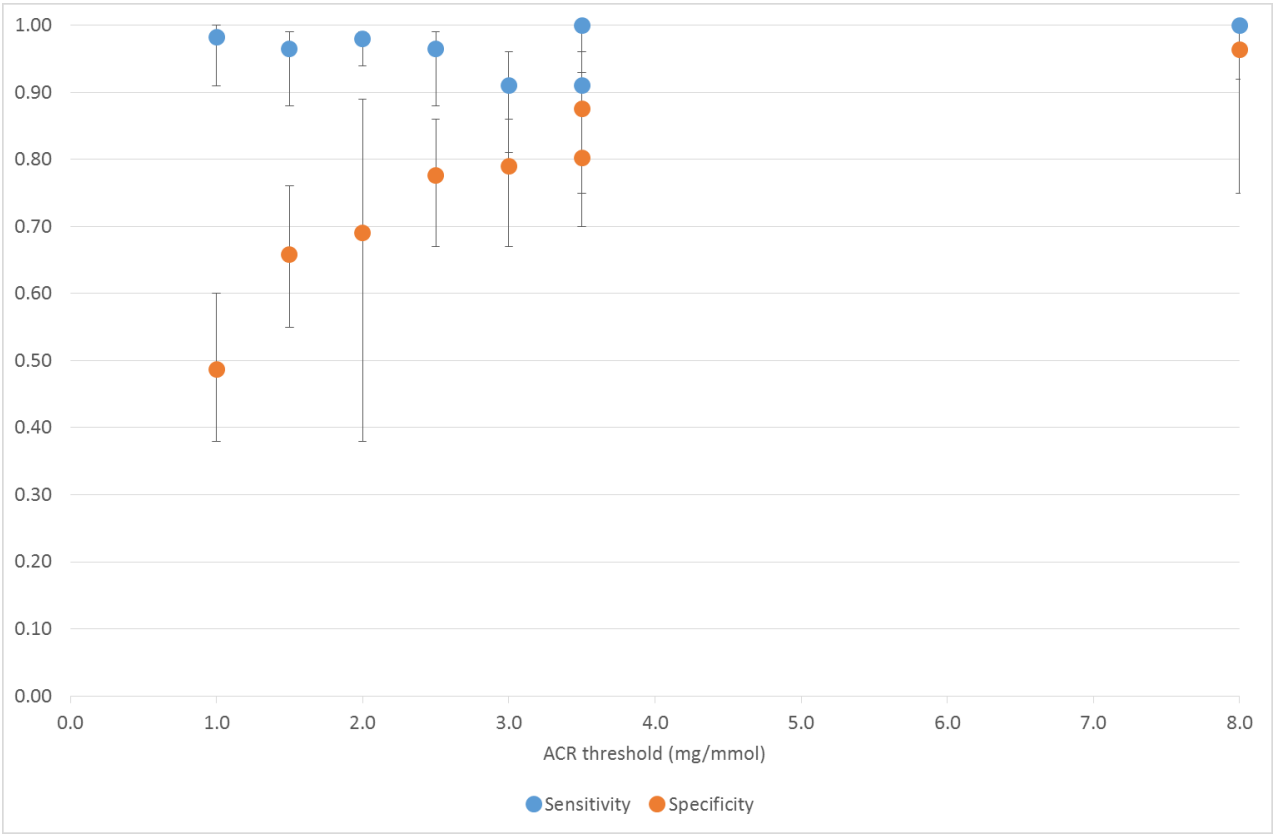
Study	Reason for exclusion
Waugh J, Hooper R, Lamb E, Robson S, Shennan A, Milne F, Price C, Thangaratinam S, Berdunov V, Bingham J. Spot protein-creatinine ratio and spot albumin-creatinine ratio in the assessment of pre-eclampsia: a diagnostic accuracy study with decision-analytic model-based economic evaluation and acceptability analysis. Health Technology Assessment 21(61) 2017	Study considers diagnosis of severe pre-eclampsia rather than the diagnosis of proteinuria.

Appendix L – Research recommendations

No research recommendations were made for this review question.

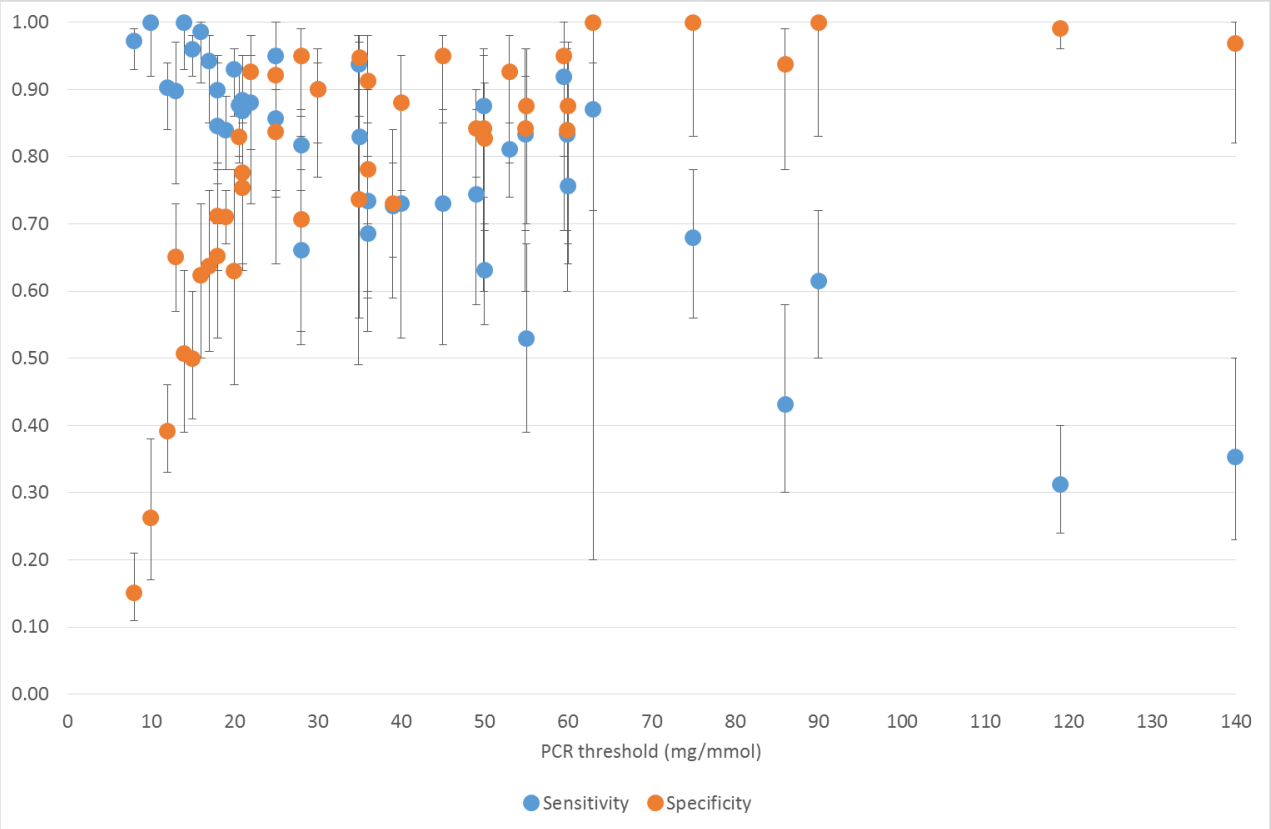
Appendix M – Additional Graphs

Figure 10: Graphical representation (scatterplot of distribution) of sensitivity and specificity for ACR at all reported thresholds (with 95% CI)



Uses meta-analysed data when available; data is not weighted by study size; ACR: albumin:creatinine ratio; CI: confidence interval;

Figure 11: Graphical representation (scatterplot of distribution) of sensitivity and specificity for PCR at all reported thresholds (with 95%CI)



Uses meta-analysed data when available; data is not weighted by study size; CI: confidence interval; PCR: protein:creatinine ratio;