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Early prognostic factors of outcomes in monochorionic twin pregnancy: systematic review and meta-analysis

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Early prognostic factors of outcomes in monochorionic twin pregnancy: systematic review and meta-analysis

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Condensation, Implications and Contributions:

- Assessment of prognostic ability of maternal characteristics, first trimester ultrasound and biomarkers to predict complications in monochorionic twin pregnancies
- No prognostic test is currently available to predict which monochorionic twin pregnancies will develop twin-twin transfusion syndrome, intrauterine growth restriction, intrauterine fetal death. Although a significant association was found between nuchal translucency >95th centile in one/both fetuses and twin-twin transfusion syndrome, and crown-rump length discordance ≥10% and twin-twin transfusion syndrome, both demonstrated poor individual prognostic ability. We have revealed a lack of research investigating first trimester biomarkers in MC twin pregnancies. Different assessment methods and definitions of each variable and outcome were an issue and this highlights the need for a large cohort study to evaluate these factors.

Short version of title: Early prognostic factors in monochorionic twin pregnancy

Abstract

Objective: Assess ability of first trimester pregnancy related factors (ultrasound measurements, maternal characteristics, biomarkers) to predict complications in monochorionic twin pregnancies

Data sources: MEDLINE, EMBASE, ISI Web of Science, CINAHL, the Cochrane Central Registration of Controlled Trials and Research Registers, and Google Scholar, from inception to 12 May 2017. Grey literature and bibliographies of articles were checked.

Study eligibility criteria: Studies that reported ultrasound measurements, maternal characteristics, or potential biomarkers, measured in the first trimester in monochorionic diamniotic twin pregnancies, where the potential prognostic ability between the variable and twin-twin transfusion syndrome, growth restriction, or intrauterine fetal death could be assessed.

Study appraisal and synthesis methods: Quality assessment was evaluated using the STROBE checklist by 2 reviewers independently. For meta-analysis, odds ratios using a random effects model, or standardized mean difference were calculated. If a moderate association was found, the prognostic ability was evaluated by calculating the sensitivity and specificity. Risk of heterogeneity was reported as I^2 and publication bias was visually assessed by funnel plots and quantitatively by Egger's test.

Results: Forty-eight studies were eligible for inclusion. Twenty meta-analyses could be performed. A moderate association was demonstrated in 3 meta-analyses, between: NT>95th centile in one/both fetuses and TTTS (OR 2.29 [95%CI 1.05, 4.96] I^2=6.6%, 4 studies, 615 pregnancies); CRL discordance ≥10% and TTTS (OR 2.43 [95%CI 1.13, 5.21] I^2=14.1%, 3 studies, 708 pregnancies); and maternal

ethnicity and TTTS (OR 2.12 [95%CI 1.17, 3.83] I^2=0.0%, 5 studies, 467 pregnancies), but none demonstrated a prognostic ability for any outcome under investigation.

Conclusions: It is not currently possible to predict adverse outcomes in monochorionic twin pregnancies. We have revealed a lack of research investigating first trimester biomarkers in monochorionic twin pregnancies. Different assessment methods and definitions of each variable and outcome were an issue and this highlights the need for a large cohort study to evaluate these factors.

Keywords: biomarker, crown-rump length, first trimester, growth restriction, maternal characteristics, monochorionic, nuchal translucency, predict, prognostic factor, twin pregnancy, twin-twin transfusion syndrome, ultrasound

Introduction

Monochorionic (MC) twin pregnancies are considered high-risk because of the potential to develop the morbid conditions of twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS), or twin oligohydramnios-polyhydramnios sequence (TOPS) (1, 2). Additionally, MC twins have a greater likelihood of developing selective intrauterine growth restriction (sIUGR), and single and double intrauterine fetal death (sIUFD and dIUFD) compared to dichorionic (DC) twins (3). Consequently, international professional guidelines advise that all MC twin pregnancies undergo ultrasound assessment of fetal growth, amniotic fluid volume, and umbilical artery Doppler velocimetry every 2 weeks from 16 weeks gestation (4-6). However, the majority of MC twins will not develop any of these complications (7).

At present, no screening test is available to predict which MC twin pregnancy will develop complications and therefore all MC twins undergo the intensive antenatal surveillance that has an impact on patients and healthcare resources.

Objectives

To assess the ability of first trimester pregnancy related factors (ultrasound measurements, maternal characteristics, biomarkers) to predict complications in MC twin pregnancies.

Methods

This systematic review was performed according to a protocol designed *a priori* and registered on PROSPERO (www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015024975). It is reported according to the PRISMA guidelines (8).

Eligibility criteria

Studies that reported ultrasound measurements, maternal characteristics, or potential biomarkers, measured in the first trimester (i.e. up to 14 weeks gestation), in monochorionic diamniotic (MCDA) twin pregnancies that provided sufficient information to assess the association between the variable and outcome were eligible for inclusion. Monochorionicity had to have been confirmed either by the presence of the 'T' sign or absence of the 'λ' or 'twin peak' sign on first trimester ultrasound (9), or postnatally by placental examination. Studies with <5 MCDA twin pregnancies were excluded, as were those pregnancies affected by: major structural

or chromosomal anomalies, twin-reversed arterial perfusion (TRAP), miscarriage, sIUFD <14 weeks gestation, higher order multiple or monoamniotic pregnancies.

Potential prognostic factors

All first trimester potential prognostic factors were included. Data were extracted using the same cut-offs as reported by the authors. For meta-analysis thresholds were not combined (i.e. crown-rump length (CRL) discordance >10% was not combined with CRL discordance >20%). Maternal age and BMI were analyzed as continuous variables. Maternal ethnicity was dichotomized to 'Caucasian' and 'non-Caucasian' to enable meta-analysis, parity was dichotomized to 'multiparous' and 'nulliparous', maternal smoking was dichotomized to current 'smoker' and 'non-smoker' with ex-smokers included in the 'non-smoker' group, and mode of conception was dichotomized to 'spontaneous' or 'assisted reproductive technology (ART)'.

Outcomes

The outcomes evaluated were:

- TTTS, irrespective of whether treatment was required/performed, and according to definitions used by authors of individual studies (see Supplementary File Table 1) including significant discrepancy in inter-twin amniotic fluid volumes as per Quintero (10).
- Antenatal growth restriction only (AGR), based on estimated fetal weight (EFW) (irrespective of the presence of umbilical artery Doppler abnormalities), as defined by each study. Regardless of definition used within individual studies, we adopted the consensus definition of ≥20% inter-twin EFW

discordance as per the American College of Obstetricians and Gynecologists (ACOG), the International Society of Ultrasound in Obstetrics & Gynecology (ISUOG) and the Royal College of Obstetricians and Gynaecologists in the UK (RCOG) (4-6).

- Postnatal growth restriction only (PGR), based on birthweight (BW) as defined by each study, but if reported as inter-twin discordance, must be ≥20%
- Antenatal and postnatal growth restriction within the same pregnancy
- Antenatal or postnatal growth restriction (AoPGR) which includes all the growth restricted pregnancies in the other three growth restriction groups (AGR, PGR, antenatal and growth restriction within the same pregnancy)
- sIUFD after 14 weeks gestation
- dIUFD after 14 weeks gestation

Within our protocol the definitions of the outcomes were not pre-specified to allow for variation of definitions. Where a definition exists e.g. Quintero for TTTS, ≥20% for antenatal growth discordance, this was adopted for decisions regarding inclusion of studies for meta-analysis. For those analyses where there was variation in definitions, sensitivity analysis was employed where possible to determine the effects of the definition on the results.

Information sources

Electronic databases were searched: MEDLINE, EMBASE, ISI Web of Science, CINAHL, the Cochrane Central Registration of Controlled Trials and Research Registers, and Google Scholar, from inception to 12 May 2017. Grey literature was hand searched and bibliographies of articles checked.

Search strategy

Keywords and MeSH terms relating to the following were used: TTTS, TAPS, TOPS, fetal death, IUGR, diseases in twins, amniotic fluid, placenta, biomarkers, ultrasonographic markers and prediction; and combined with “monochorionic” and “twins” (Appendix A).

Study selection and data extraction

Manuscripts to be included in the review were selected by two reviewers (FLM, MJH) independently in a two stage process; the first being review of titles and abstracts for selection for the second stage of full manuscript review. Where there was disagreement consensus was reached by a third reviewer (RKM). There was no restriction on language or study design. Abstracts were included if there was sufficient information to assess the study quality and association between the variable and the outcome. Data were extracted independently by FLM and MJH and any discrepancies resolved by RKM and MDK. Authors were contacted to clarify information as required.

Quality assessment of included studies

The quality of the studies was assessed by FLM and MJH using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) tool (11) as this was considered most appropriate as the majority of studies were observational. It was not possible to use the recommended quality checklists for prognostic factor research (12) e.g. Quality in Prognosis Studies (QUIPS) (13), REMARK (14), nor diagnostic studies Quality Assessment of Diagnostic Accuracy Studies (QUADAS)

(15) due to the large number of included studies that were not focused on the prognostic value of factors.

Assessment of heterogeneity

Forest plots were created to visually assess outliers and any unusual results were investigated with sensitivity analysis. The I^2 value was calculated for each meta-analysis. A measurement ≥50% indicated a substantial risk of heterogeneity. Where there was significant heterogeneity (visually or statistically), a sensitivity analysis was performed to assess the effect.

Assessment of reporting bias

In meta-analyses with >10 studies, a funnel plot was generated using the *metafunnel* command (16) in Stata (Stata, 2015 Release 13.1 StataCorp, Texas, USA), and Egger's test was performed using the *metabias* command (17), and with a significance level of 10%.

Data synthesis

Meta-analyses were reported at the per pregnancy level, not per fetus for two reasons. Firstly, reporting at the fetus level would require an adjustment for clustering, but more importantly when considering prognostic factors for pregnancy related diseases in multiple pregnancy, any change in management due to a prognostic test/model would be effected at the pregnancy level.

Data synthesis for factors reported as means and medians

For continuous data with a normal distribution, medians were converted to means to enable meta-analysis. When the interquartile range (IQR) was reported, the standard deviation (SD) was calculated as IQR/1.35 (18). When medians were not reported with IQRs, the mean and SD was estimated (19). For non-normally distributed data (NT discordance, CRL discordance and parity) where only the median was reported, it was not possible to convert the median to means, therefore these results could not be included in meta-analysis.

Data synthesis for association

Data were extracted to create 2x2 contingency tables to compare: a) disease vs. no disease but where other complications may be present, and b) disease vs. normal pregnancy where no complications were present at all. For outcomes with more than three included studies, odds ratios (OR) were calculated using the *metan* command (20) in Stata, and pooled using the DerSimonian-Laird random effects model to account for expected clinical heterogeneity. ORs >2 were considered to demonstrate a moderate association (21), thus the prognostic ability of the factor was subsequently investigated. For continuous variables reported as, or converted into, means and SDs, the standardized mean difference (SMD) was calculated using the *metan* command in Stata. SMDs ≥0.5 were considered to demonstrate a moderate effect (22) and the prognostic ability of the factor was investigated.

Data synthesis for prognostic ability

Bivariate meta-analysis using a random effects model was performed in analyses of more than three studies to calculate the summary sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) using the *metandi* command

(23) in Stata. Hierarchical Summary Receiver Operating Characteristic (HSROC) curves were generated using the *metandiplot* command (23) to represent the level of uncertainty of sensitivity and specificity for bivariate analyses. Univariate analysis was carried out for analyses with less than four studies using MetaDiSc (v1.4116, Madrid, Spain)(24), with symmetrical Summary Receiver Operating Characteristic (SROC) curves generated. 0.5 was added to cells of 0 to perform univariate meta-analysis, but not bivariate meta-analysis, due to the necessary use of different computer programs. When a prognostic factor was found to have a moderate association with the outcome, the predictive ability was investigated and the post-test probability using Fagan's nomogram (25), which accounts for pre-test probability, was calculated.

Results

Study selection

Electronic searches identified 2439 citations of which 1312 titles were excluded after review of titles and 743 after abstract review. The full papers of the remaining 384 full articles were assessed (Figure 1) of which 48 studies (26-73) met the inclusion criteria equating to the evaluation of 5365 MC twin pregnancies. See Supplementary File Table 1 for the Study Characteristics of all included studies. Studies that met the inclusion criteria but were unable to be included in meta-analysis are described in Appendix B, as are individual prognostic factors that were unable to be included in meta-analysis.

Figure 1 about here please

Study characteristics

Supplementary File Table 1 displays the study characteristics of the included articles and details regarding individual measurements such as definitions of growth restriction. The ultrasound measurements reported were: nuchal translucency (NT), crown rump length (CRL), the presence of reversed a wave in the ductus venosus, and umbilical venous flow velocity. The maternal characteristics reported in eligible studies were: maternal age, ethnicity, BMI, parity and smoking. Mode of conception and fetal gender was also reported. The first trimester biomarkers reported were all from maternal serum, and included: thyroid stimulating hormone (TSH), free thyroxine (FT4), β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A). The most frequently investigated outcomes were TTTS (n=31 studies), antenatal growth restriction (n=14 studies), and postnatal growth restriction (n=12 studies).

*Figure 2 about here please**

Risk of bias of included studies

Most studies were not designed for the recruitment of participants to examine first trimester potential prognostic factors. The different aspects of the 'STROBE' classification are demonstrated in Figure 2. Of note is that the studies were poor at stating how they addressed missing data, and which data were missing. One aspect of the study design that may increase the risk of heterogeneity was that different control groups were used: (i) MC twin pregnancies with no maternal or fetal complications, (ii) MC twins with no fetal complications, (iii) other MC twin pregnancies in the study who did not have the condition being examined but did

have other MC complications. For the GR outcomes, studies were classified according to the time that the growth measurement was performed, meaning that 5 studies (32, 37, 41, 71, 72) despite calling their outcome IUGR, were included in the PGR group as their definition was based on birthweights, not antenatal ultrasound measurements. In calculating discordance between estimated fetal weight or birthweight all studies used the larger measure as the denominator. Four studies included in the PGR meta-analyses only measured abnormal growth by BWD, Moriichi et al.(56), Stagnati et al.(62), Sun et al.(64), Zhao et al.(72), meaning that both babies may have weighed >10th centile . All other studies that reported abnormal growth as an outcome had to have at least one fetus/baby <10th centile, except for three studies that were not able to be included in meta-analyses due to being the only studies which measured their potential prognostic factor (42, 45, 52). Not all the participants in the study by Murakami et al.(57) had delivered at the time the study was published, therefore only those who had delivered were included in our analysis. Only one funnel plot and Egger's test was required, that did suggest significant publication bias in the maternal age and TTTS analysis (available on request from authors).

Synthesis of results

Meta-analysis could be performed for the following prognostic factors:

a) Ultrasound measurements: NT >95th centile in one/both fetuses, NT discordance ≥20%, CRL discordance ≥10%.
b) Maternal characteristics: age, ethnicity, BMI, parity, smoking, mode of conception, fetal gender.

In total, 20 separate meta-analyses were performed; of these, 3 demonstrated a moderate association (OR >2), but none demonstrated a prognostic ability for any outcome under investigation. The results we present here are for the potential prognostic factors with a moderate or strong association with an outcome. All other results are available in Appendix C. Meta-analysis was unable to be performed on first trimester biomarkers because of the way the data were presented. An insufficient number of studies reported antenatal and postnatal growth restriction within the same pregnancy (27, 35), and IUFD as outcomes to include in meta-analysis (results available from authors on request). Only 4 studies (26, 34, 55, 69) used a control group of 'normal' pregnancies, the other 44 studies used a control group of 'no disease under investigation' e.g. TTTS vs no TTTS, therefore the results should be considered as comparing to 'no disease'

Insert table 1 about here please

NT>95th centile in one/both fetuses and TTTS

A significant association between NT>95th centile in one/both fetuses and TTTS was found (OR 2.29 [95%CI 1.05, 4.96] I^2=6.6%, 4 studies, 615 pregnancies) (Figure 3a). Bivariate meta-analysis results are in table 1. The post-test probability of a positive result was 0.22 (95%CI 0.13, 0.35), and a negative result was 0.14 (95%CI 0.13, 0.15), assuming pre-test probability of 0.176 based on a prevalence of 15%. See Figure 3b for the HSROC that shows reasonable specificity but poor sensitivity.

Figures 3a and 3b about here please

CRL discordance ≥10% and TTTS

A significant association between CRL discordance ≥10% and TTTS was found (OR 2.43 [95%CI 1.13, 5.21] I^2=14.1%, 3 studies, 708 pregnancies) (Figure 4a). Univariate meta-analysis results are in table 1. The post-test probability of a positive result was 0.28 (95%CI 0.20, 0.38), and a negative result was 0.13 (95%CI 0.12, 0.15), assuming pre-test probability of 0.176 based on a prevalence of 15%. See Figure 4b for the SROC.

Figures 4a and 4b about here please

Maternal ethnicity and TTTS

An OR >1 indicated a higher-risk of TTTS if the woman was Caucasian, and an OR <1 indicated a higher-risk of TTTS if the woman was non-Caucasian. A significant association between maternal ethnicity and TTTS was found (OR 2.12 [95%CI 1.17, 3.83] I^2=0.0%, 5 studies, 467 pregnancies) (Figure 5a). Bivariate meta-analysis results are in table 1. The post-test probability of a positive result was 0.17 (95%CI 0.15, 0.19), and a negative result was 0.10 (95%CI 0.06, 0.16), assuming pre-test probability of 0.176 based on a prevalence of 15%. See Figure 5b for HSROC that shows moderate sensitivity but poor specificity.

Figures 5a and 5b about here please

Discussion

Main findings

This is the first systematic review to look at first trimester potential prognostic factors for growth restriction in MC twins, and explore maternal characteristics and first trimester maternal serum biomarkers as prognostic factors for TTTS. Although a significant association was found between NT>95th centile in one/both fetuses and TTTS, and CRL discordance ≥10% and TTTS, both demonstrated poor individual prognostic ability. A moderate significant association between maternal ethnicity and TTTS was found, with Caucasian women more likely to develop TTTS, but as there is no plausible biological mechanism for this association thus this may reflect the lack of diversity within the study populations and publication bias. The other first trimester ultrasound measurements and maternal characteristics demonstrated no association with adverse outcomes.

Only 2 studies examined first trimester maternal serum biomarkers, with Ashoor et al.(26) finding no significant difference in TSH, FT4 or β-hCG in those pregnancies that developed TTTS, and Linskens (48) noting a trend towards increased β-hCG and PAPP-A levels in those pregnancies that developed TTTS. As Linskens only reported the median and not the IQR these studies could not be combined in meta-analysis, but this warrants further investigation due to the small study sizes and biological plausibility of β-hCG and PAPP-A being implicated in TTTS as markers of placental function.

Strengths and limitations

A major strength of our study was to include all possible prognostic factors and perform a robust statistical analysis to look at the association and prognostic ability of the factors. The search strategy was as inclusive as possible, and there was no limit on language. It was particularly important to look at modifiable factors such as

smoking and maternal BMI where lifestyle changes may be associated with a lower risk for adverse outcome.

One limitation of our review was the different definitions that studies used for their control groups, variables and outcomes, which is why we did not stipulate the individual definitions rigidly prior to commencing the search. This was an issue for growth restriction as there is currently no validated standard definition of abnormal growth in MC twins. Consequently, the included studies defined growth restriction in a myriad of ways: abdominal circumference (AC) ≤5th centile, EFW <10th centile, EFW <5th centile, EFWD >20%, LBW <10th centile, LBW <5th centile, BWD ≥20%, BWD ≥25%, and in different combinations of in one twin, or both twins when not measuring discordance, all of which can be associated with adverse outcome. This issue has attempted to be investigated by a recent Delphi consensus looking at selective fetal growth restriction in twin pregnancy (74), and will be addressed by the creation of a 'Core Outcome Set' for 'selective fetal growth restriction in twin pregnancies'(75) which is due to be completed by August 2019. In this systematic review, we attempted to address the problem by creating different growth restriction groups so as to be as inclusive as possible. The AGR group reflects real life and is what obstetricians base their management on. However, ultrasound scanning and calculation of EFWD only has a moderate ability to detect BWD with a recent systematic review reporting a sensitivity of 65.4% (95%CI 57.9, 72.3) and specificity of 90.8% (95%CI 87.1, 93.5%) for EFWD ≥20% predicting BWD ≥20%, although the analysis does include DC and MC twins(76). Therefore, the PGR group was included as an absolute measure, which avoids scan error. However, there is controversy whether BWD is reflective of pathological growth, and indeed what the cut-off should be. A recent meta-analysis, that also highlighted the problem of different definitions

of abnormal growth in twins, demonstrated that MC twins with BWD ≥20% (which also included EFWD ≥20%) had a higher risk of IUFD than concordant MC twins (OR 2.8 [95%CI 1.3,5.8] 6 studies, 1286 pregnancies, I^2 not reported) (77). Currently, MC twins with isolated BWD are not managed differently neonatally as this is guided by the actual birthweight. Additionally, BWD is not always reflective of IUGR with 21.1% of pregnancies with BWD ≥20% not including at least one fetus with an EFW <10th centile, and 21% of pregnancies with at least one fetus with an EFW <10th centile not demonstrating concurrent BWD(78). However, most studies in our search that reported growth based on postnatal measures used BWD as opposed to LBW, therefore it was decided to include BWD in our systematic review. The use of inter-twin growth discordance in isolation, whether EFWD or BWD, also presents the problem of missing pregnancies where both twins are growth restricted, but irrespective of choice of definition and cut-offs, all growth outcomes have the common problem of not being based on specific twin growth charts, which until July 2017 did not exist. Since performing this review, twin growth charts have been launched in the UK to enable more accurate assessment of twin fetal growth (79). Another issue was that of cut-offs for the variables as the cut-offs have not been appropriately validated and may not be appropriate for the study's patient population, or the conditions being explored. We had planned to compare a) disease vs. no disease but where other complications may be present, and b) disease vs. normal pregnancy where no complications were present at all however as most studies used the former control group, we were unable to perform a separate analysis for the latter comparison. This has only allowed us to evaluate the ability of each potential prognostic factor to predict a specific condition, and not any condition (and thus we cannot predict the chance of the pregnancy being completely 'normal').

Comparison with existing literature

A systematic review evaluating prognostic factors up to 16 weeks for TTTS has recently been published, however they only looked at ultrasound prognostic markers, and their search was up to April 2014 (80). They stated that an increased risk of TTTS was associated with inter-twin NT discrepancy, NT>95th centile, and CRL discrepancy, but similar to our results, the prognostic ability of these factors was low. In addition to our inclusion of other MC twin complications, there are other differences between our reviews, including that Stagnati et al. did not exclude pregnancies with chromosomal/structural anomalies that affect first trimester ultrasound measurements. D'Antonio et al. performed a systematic review examining the ability of first trimester CRL discordance ≥10% to predict BWD ≥20%, preterm birth, fetal anomalies, IUFD and neonatal death, and found it also had a low prognostic ability for all outcomes (81).

Conclusions and Implications

The main clinical implication of the results of our systematic review is that they support the guidance from the Royal College of Obstetricians and Gynaecologists (RCOG) that 'screening for TTTS by first trimester NT measurements should not be offered'(5). Although we have shown significant associations between first trimester variables and subsequent pregnancy outcome, the prognostic ability of each individual variable is poor, thus the results do not suggest their use to screen MC pregnancies in clinical practice.

However, we have identified a gap in knowledge which has implications for research as most studies able to be included in the systematic review were not designed with the intention of assessing first trimester prognostic factors for subsequent outcomes in MC twins. Consequently, we designed the OMMIT study (ISRCTN13114861) a

large cohort study, purposefully-designed to investigate potential prognostic factors and explore novel prognostic markers that have not previously been evaluated: including alpha-fetoprotein (AFP) , pregnancy-associated plasma protein A (PAPP-A), and s-Flt-1 (82). To avoid the problem of using non-validated cut-offs, variables should be kept continuous and not dichotomized.

Conclusion

We have investigated the association and prognostic ability of first trimester factors, including maternal characteristics, associated with TTTS, growth restriction and IUFD. We have found that it is not currently possible to predict adverse outcomes in MC twin pregnancies, and have revealed a lack of research investigating first trimester biomarkers in MC twin pregnancies. Different assessment methods and definitions of each variable and outcome were an issue and this highlights the need for a large cohort study to evaluate these factors.

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References

Tables

Table 1 Summary of accuracy of prognostic factors with a significant association with twin-twin transfusion syndrome

Prognostic factor	Sensitivity (95%CI)	Specificity (95%CI)	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)
NT>95th centile in one/both fetuses*	0.118 (0.035, 0.330)	0.926 (0.882, 0.954)	1.589 (0.589, 4.290)	0.953 (0.830, 1.094)
CRL discordance ≥10%†	0.203 (0.120, 0.308)	0.908 (0.882, 0.929)	2.180 (1.147, 4.142)	0.904 (0.794, 1.030)
Maternal ethnicity*	0.826 (0.672, 0.917)	0.278 (0.135, 0.917)	1.145 (0.941, 1.394)	0.624 (0.349, 1.117)

*Analysed by bivariate analysis. †Analysed by univariate analysis. CRL: crown-rump length, NT: nuchal translucency

Figure legend

Figure 1 Flow diagram of study inclusion

Figure 2 Quality assessment of included studies according to 'Strengthening The Reporting of Observational studies in Epidemiology' (STROBE) checklist

Figure 3a Forest plot of association between NT>95th centile (NT>95th) in one/both fetuses and twin-twin transfusion syndrome (TTTS)

Figure 3b Hierarchical summary receiver operating characteristic curves (HSROC) for NT>95th centile in one/both fetuses and twin-twin transfusion syndrome (TTTS) studies. This visually represents the global summary of prognostic factor performance by plotting the mean sensitivity against the reversed mean specificity produced by the bivariate analysis. The ellipses represent the 95% confidence intervals of the mean sensitivities and specificities and 95% prediction region. The closer the values are to the top left corner, the greater the accuracy of the prognostic factor.

Figure 4a Forest plot of association between crown-rump length discordance ≥10% (CRLD>10%) and twin-twin transfusion syndrome (TTTS)

Figure 4b Summary receiver operating characteristic curves for crown-rump length discordance ≥10% and twin-twin transfusion syndrome

Figure 5a Forest plot of association between maternal ethnicity and twin-twin transfusion syndrome (TTTS)

Figure 5b Hierarchical summary receiver operating characteristic curves for maternal ethnicity and twin-twin transfusion syndrome studies. This visually represents the global summary of prognostic factor performance by plotting the mean sensitivity against the reversed mean specificity produced by the bivariate analysis. The ellipses represent the 95% confidence intervals of the mean sensitivities and specificities and 95% prediction region. The closer the values are to the top left corner, the greater the accuracy of the prognostic factor.

References

1. Moldenhauer J, Johnson M. Diagnosis and management of complicated monochorionic twins. Clinical obstetrics and gynecology. 2015;58(3):632-42.
2. Sebire NJ, Snijders RJM, Hughes K, Sepulveda W, Nicolaides KH. The hidden mortality of monochorionic twin pregnancies. Br J Obstet Gynecol. 1997;104(10):1203-7.

3. Hillman S, Morris R, Kilby M. Co-twin prognosis after single fetal death: a systematic review and meta-analysis. Obstet Gynecol. 2011;118(4):928-40.
4. ACOG. Practice bulletin No. 169: Multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. Obstet Gynecol. 2016;128(4):e131-46.
5. Kilby M, Bricker L. RCOG Green-top Guideline No. 51: Management of monochorionic twin pregnancy. BJOG. 2016.
6. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, et al. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. Ultrasound Obstet Gynecol. 2016;47(2):247-63.
7. Lewi L, Jani J, Blickstein I, Huber A, Gucciardo L, Van Mieghem T, et al. The outcome of monochorionic diamniotic twin gestations in the era of invasive fetal therapy: a prospective cohort study. Am J Obstet Gynecol. 2008;199(5):514.e1-.e8.
8. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339.
9. Sepulveda W, Sebire N, Hughes K, Odibo A, KH N. The lambda sign at 10–14 weeks of gestation as a predictor of chorionicity in twin pregnancies. Ultrasound Obstet Gynecol. 1996;7:421-23.
10. Quintero R, Morales W, Allen M, Bornick O, Johnson P, Kruger M. Staging of twin-twin transfusion syndrome. J Perinatol. 1999;19:550-5.
11. von Elm E, Altman D, Egger M, Pocock S, Gøtzsche P, Vandenbroucke J, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.
12. Riley R, Hayden J, Steyerberg E, Moons K, Abrams K, Kyzas P, et al. Prognosis research strategy (PROGRESS) 2: Prognostic factor research. PLoS Med. 2013;10(2):1-9.
13. Hayden J, van der Windt D, Cartwright J, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.
14. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. Reporting recommendations for tumor marker prognostic studies (REMARK). Journal of the National Cancer Institute. 2005;97(16):1180-4.
15. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
16. Sterne J. METAFUNNEL: Stata module to produce funnel plots for meta-analysis Statistical Software Components S434101. Boston: Boston College Department of Economics; 2003.
17. Harbord R, Harris R, Sterne J, T. S. METABIAS: Stata module to test for small-study effects in meta-analysis. Statistical Software Components S404901. Boston: Boston College Department of Economics; 2009.
18. Cochrane. 7.7.3.5 Medians and interquartile ranges. Cochrane Handbook for Systematic Reviews of Interventions2011.
19. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5(1):13.
20. Harris R, Bradburn M, Deeks J, Harbord R, Altman D, T S, et al. METAN: Stata module for fixed and random effects meta-analysis. Statistical Software Components S456798. Boston: Boston College Department of Economics; 2009.
21. Morris RK, Meller CH, Tamblyn J, Malin GM, Riley RD, Kilby MD, et al. Association and prediction of amniotic fluid measurements for adverse pregnancy outcome: systematic review and meta-analysis. Br J Obstet Gynecol. 2014;121(6):686-99.
22. Cohen J. Statistical power analysis for the behavioural sciences. New York: Academic Press Inc; 1977.
23. Harbord R. METANDI: Stata module to perform meta-analysis of diagnostic accuracy. . Statistical Software Components S456932. Boston: Boston College Department of Economics; 2008.
24. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol. 2006;6:31-.
25. Fagan T. Nomogram for Bayes's Theorem. N Engl J Med. 1975;293(5):257-.
26. Ashoor G, Muto O, Poon L, Muhaisen M, Nicolaides K. Maternal thyroid function at gestational weeks 11-13 in twin pregnancies. Thyroid. 2013;23(9):1165-71.
27. Bajoria R, Sooranna SR, Ward S, Chatterjee R. Elevated IGFBP-1 cause high bone turnover in growth-restricted monochorionic twins with discordant birth weight. Bone. 2006;38(6):929-34.
28. Bajoria R, Sooranna SR, Chatterjee R. Leptin and bone turnover in monochorionic twins complicated by twin-twin transfusion syndrome. Osteoporos Int. 2007;18(2):193-200.

29. Baraa Allaf M, Vintzileos AM, Chavez MR, Wax JA, Ravangard SF, Figueroa R, et al. First-trimester sonographic prediction of obstetric and neonatal outcomes in monochorionic diamniotic twin pregnancies. J Ultrasound Med. 2014;33(1):135-40.
30. Ben-Ami I, Molina FS, Battino S, Daniel-Spiegel E, Melcer Y, Flock A, et al. Monochorionic diamniotic in vitro fertilization twins have a decreased incidence of twin-to-twin transfusion syndrome. Fertil Steril. 2016;105(3):729-33.
31. Carver A, Haeri S, Moldenhauer J, Wolfe HM, Goodnight W. Monochorionic diamniotic twin pregnancy: timing and duration of sonographic surveillance for detection of twin-twin transfusion syndrome. J Ultrasound Med. 2011;30(3):297-301.
32. Chai H, Luo Y, Huang X, Zhou Y, Fang Q. Perinatal outcome of monochorionic diamniotic twins with selective intrauterine growth restriction. Zhonghua Fu Chan Ke Za Zhi. 2013;48(6):416-20.
33. Chang YL, Chang SD, Chao AS, Hsieh PC, Wang CN, Wang TH. Clinical outcome and placental territory ratio of monochorionic twin pregnancies and selective intrauterine growth restriction with different types of umbilical artery Doppler. Prenat Diagn. 2009;29(3):253-6.
34. Chang YL, Chao AS, Peng HH, Chang SD, Su SY, Chen KJ, et al. Increased fetal plasma erythropoietin in monochorionic twin pregnancies with selective intrauterine growth restriction and abnormal umbilical artery doppler. Twin Res Hum Genet. 2016;19(4):383-8.
35. Chang Y-L, Wang T-H, Abufraijeh SM, Chang S-D, Chao A-S, Hsieh PCC. Preliminary report of altered insulin secretion pattern in monochorionic twin pregnancies complicated with selective intrauterine growth restriction. Taiwan J Obstet Gynecol. 2017;56(1):51-4.
36. Cosmi E, Visentin S, Favretto D, Tucci M, Ragazzi E, Viel G, et al. Selective intrauterine growth restriction in monochorionic twin pregnancies: Markers of endothelial damage and metabolomic profile. Twin Res Hum Genet. 2013;16(4):816-26.
37. El Kateb A, Nasr B, Nassar M, Bernard JP, Ville Y. First-trimester ultrasound examination and the outcome of monochorionic twin pregnancies. Prenat Diagn. 2007;27(10):922-5.
38. Flock A, Reinsberg J, Berg C, Gembruch U, Geipel A. Impact of chorionicity on first-trimester nuchal translucency screening in ART twin pregnancies. Prenat Diagn. 2013;33(8):722-5.
39. Fratelli N, Prefumo F, Fichera A, Valcamonico A, Marella D, Frusca T. Nuchal translucency thickness and crown rump length discordance for the prediction of outcome in monochorionic diamniotic pregnancies. Early Hum Dev. 2011;87(1):27-30.
40. Fujioka K, Mizobuchi M, Sakai H, Iwatani S, Wada K, Yoshimoto S, et al. N-terminal pro-brain natriuretic peptide levels in monochorionic diamniotic twins with selective intrauterine growth restriction. J Perinatol. 2014;34(1):6-10.
41. Ghalili A, McLennan A, Pedersen L, Kesby G, Hyett J. Outcomes of monochorionic diamniotic twin pregnancies: A comparison of assisted and spontaneous conceptions. Aust N Z J Obstet Gynaecol. 2013;53(5):437-42.
42. Johansen M, Oldenburg A, Rosthøj S, Maxild J, Rode L, Tabor A. Crown−rump length discordance in the first trimester: a predictor of adverse outcome in twin pregnancies? Ultrasound Obstet Gynecol. 2014;43(3):277-83.
43. Kagan KO, Gazzoni A, Sepulveda-Gonzalez G, Sotiriadis A, Nicolaides KH. Discordance in nuchal translucency thickness in the prediction of severe twin-to-twin transfusion syndrome. Ultrasound Obstet Gynecol. 2007;29(5):527-32.
44. Kusanovic JP, Romero R, Espinoza J, Nien JK, Kim CJ, Mittal P, et al. Twin-to-twin transfusion syndrome: an antiangiogenic state? Am J Obstet Gynecol. 2008;198(4):382.e1-.e8.
45. Lewi L, Gucciardo L, Huber A, Jani J, Van Mieghem T, Done E, et al. Clinical outcome and placental characteristics of monochorionic diamniotic twin pairs with early- and late-onset discordant growth. Am J Obstet Gynecol. 2008a;199(5):511.e1-7.
46. Lewi L, Lewi P, Diemert A, Jani J, Gucciardo L, Van Mieghem T, et al. The role of ultrasound examination in the first trimester and at 16 weeks' gestation to predict fetal complications in monochorionic diamniotic twin pregnancies. Am J Obstet Gynecol. 2008b;199(5):493.e1-7.
47. Linskens I, de Mooij Y, Twisk J, Kist W, Oepkes D, van Vugt J. Discordance in nuchal translucency measurements in monochorionic diamniotic twins as predictor of twin-to-twin transfusion syndrome. Twin Res Hum Genet. 2009;12(6):605-10.
48. Linskens IH, Engels M, Oepkes D, Heijboer AC, Blankenstein MA, van Vugt JM. A trend toward increased first trimester free beta-hCG and PAPP-A in monochorionic twins complicated by twin-to-twin transfusion syndrome. Prenat Diagn. 2010;30(9):909-10.
49. Maiz N, Staboulidou I, Leal A, Minekawa R, Nicolaides K. Ductus venosus Doppler at 11 to 13 weeks of gestation in the prediction of outcome in twin pregnancies. Obstet Gynecol. 2009;113(4):860-65.

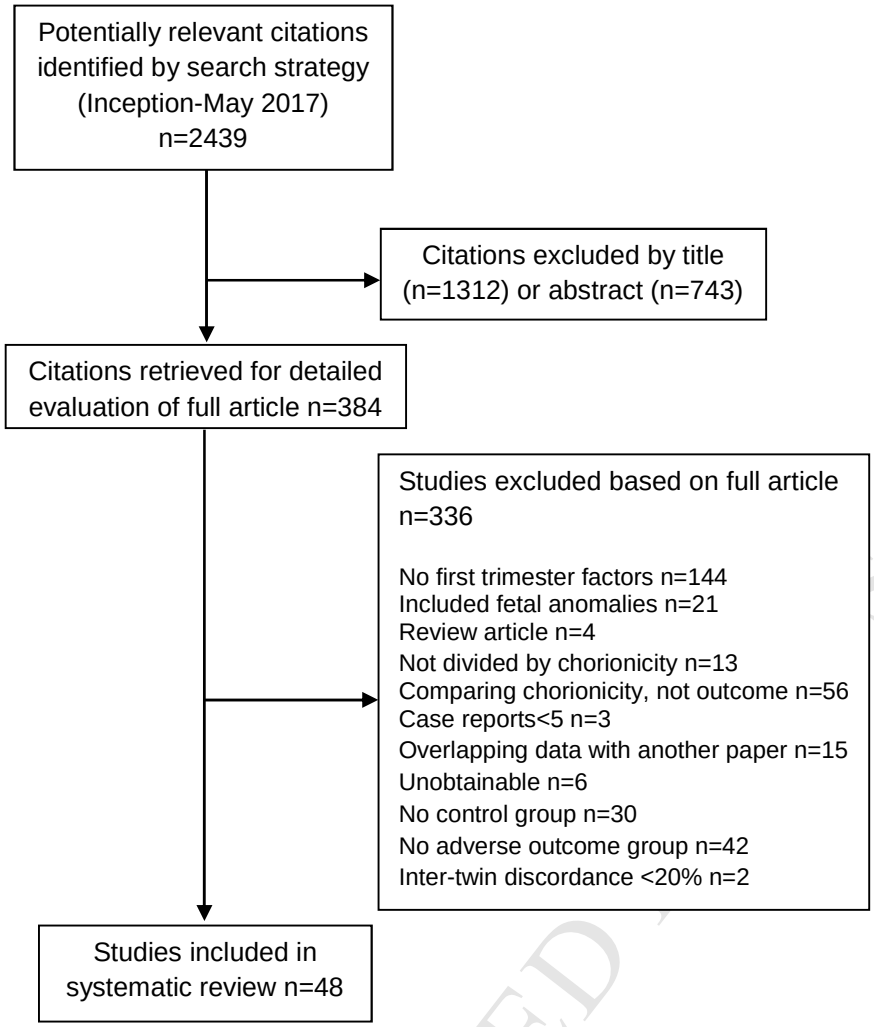
50. Matias A, Ramalho C, Montenegro N. Search for hemodynamic compromise at 11-14 weeks in monochorionic twin pregnancy: Is abnormal flow in the ductus venosus predictive of twin-twin transfusion syndrome? J Matern Fetal Neonatal Med. 2005;18(2):79-86.
51. Matias A, Montenegro N, Loureiro T, Cunha M, Duarte S, Freitas D, et al. Screening for twin–twin transfusion syndrome at 11–14 weeks of pregnancy: the key role of ductus venosus blood flow assessment. Ultrasound Obstet Gynecol. 2010;35(2):142-8.
52. Matias A, Maiz N, Montenegro N, Nicolaides K. Ductus venosus flow at 11-13 weeks in the prediction of birth weight discordance in monochorionic twins. J Perinat Med. 2011;39(4):467-70.
53. McDonald R, Hodges R, Knight M, Teoh M, Edwards A, Neil P, et al. Optimal interval between ultrasound scans for the detection of complications in monochorionic twins. Fetal Diagn Ther. 2017;41(3):197-201.
54. Miura K, Higashijima A, Miura S, Mishima H, Yamasaki K, Abe S, et al. Predominantly placenta-expressed mRNAs in maternal plasma as predictive markers for twin-twin transfusion syndrome. Prenat Diagn. 2014;34(4):345-9.
55. Memmo A, Dias T, Mahsud-Dornan S, Papageorghiou A, Bhide A, Thilaganathan B. Prediction of selective fetal growth restriction and twin-to-twin transfusion syndrome in monochorionic twins. Br J Obstet Gynecol. 2012;119(4):417-21.
56. Moriichi A, Cho K, Furuse Y, Akimoto T, Kaneshi Y, Yamada T, et al. B-type natriuretic peptide levels are correlated with birth-weight discordance in monochorionic-diamniotic twins without twin-twin transfusion syndrome. J Perinatol. 2013;33(3):182-7.
57. Murakami M, Iwasa T, Kiyokawa M, Takahashi Y, Morine M. Investigation of the factors affecting the perinatal outcome of monochorionic diamniotic twins. Arch Gynecol Obstet. 2011;283(6):1239-43.
58. Sarais V, Paffoni A, Baffero GM, Parazzini F, Persico N, Somigliana E. Estimating the risk of monochorionic twins in IVF pregnancies from the perspective of a prenatal diagnosis unit. Twin Res Hum Genet. 2015;19(1):66-71.
59. Schrey S, Kingdom J, Baczyk D, Fitzgerald B, Keating S, Ryan G, et al. Leptin is differentially expressed and epigenetically regulated across monochorionic twin placenta with discordant fetal growth. Mol Hum Reprod. 2013;19(11):764-72.
60. Sebire NJ, Souka A, Skentou H, Geerts L, Nicolaides KH. Early prediction of severe twin-to-twin transfusion syndrome. Hum Reprod. 2000;15(9):2008-10.
61. Sooranna SR, Ward S, Bajoria R. Fetal leptin influences birth weight in twins with discordant growth. Pediatr Res. 2001;49(5):667-72.
62. Stagnati V, Pagani G, Fichera A, Prefumo F. Intertwin discrepancy in middle cerebral artery peak systolic velocity and third-trimester fetal growth restriction in monochorionic–diamniotic twin pregnancy. Ultrasound Obstet Gynecol. 2016;48(1):66-71.
63. Sueters M, Middeldorp JM, Lopriore E, Oepkes D, Kanhai HH, Vandenbussche FP. Timely diagnosis of twin-to-twin transfusion syndrome in monochorionic twin pregnancies by biweekly sonography combined with patient instruction to report onset of symptoms. Ultrasound Obstet Gynecol. 2006;28(5):659-64.
64. Sun L, Zhou J, Wang K, Wang J, Shang L, Zhang J, et al. Placental up-regulation of leptin and ARMS2 is associated with growth discordance in monochorionic diamniotic twin pregnancies. Twin Res Hum Genet. 2017;20(2):169-79.
65. Tai J, Grobman WA. The association of crown-rump length discordance in twin gestations with adverse perinatal outcomes. Am J Obstet Gynecol. 2007;197(4):369 e1-4.
66. Taylor-Clarke MC, Matsui H, Roughton M, Wimalasundera RC, Gardiner HM. Ventricular strain changes in monochorionic twins with and without twin-to-twin transfusion syndrome. Am J Obstet Gynecol. 2013;208(6):462.e1-.e6.
67. Torres-Torres C, Perez-Borbon G, Benavides-Serralde JA, Guzman-Huerta ME, Hernandez-Andrade E. Prevalence and complications of monochorionic diamniotic twin pregnancy. Ginecol Obstet Mex. 2010;78(3):181-6.
68. Velayo C, Calvo JR, Sato N, Kimura Y, Yaegashi N, Nicolaides K. Evaluation of cardiac performance by abdominal fetal ECG in twin-to-twin transfusion syndrome. Prenat Diagn. 2012;32(11):1059-65.
69. Yinon Y, Ben Meir E, Berezowsky A, Weisz B, Schiff E, Mazaki-Tovi S, et al. Circulating angiogenic factors in monochorionic twin pregnancies complicated by twin-to-twin transfusion syndrome and selective intrauterine growth restriction. Am J Obstet Gynecol. 2014;210(2):141.e1-.e7.
70. Zanardini C, Prefumo F, Fichera A, Botteri E, Frusca T. Fetal cardiac parameters for prediction of twin-to-twin transfusion syndrome. Ultrasound Obstet Gynecol. 2014;44(4):434-40.

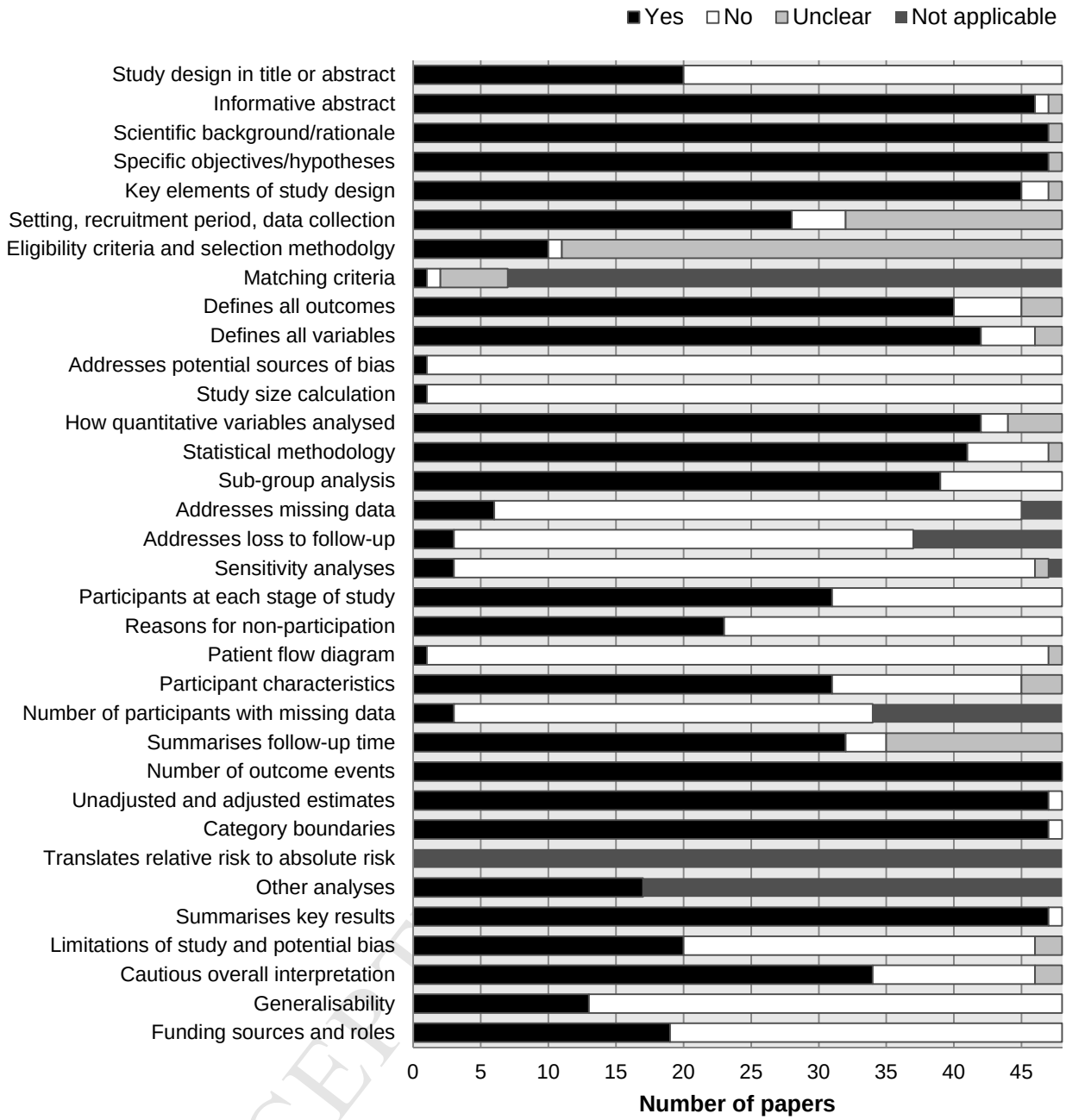
71. Zhang GL, He ZM, Shi XM, Gou CY, Gao Y, Fang Q. Discordant HIF1A mRNA levels and oxidative stress in placental shares of monochorionic twins with selective intra-uterine growth restriction. Placenta. 2015;36(3):297-303.
72. Zhao DP, de Villiers SF, Slaghekke F, Walther FJ, Middeldorp JM, Oepkes D, et al. Prevalence, size, number and localization of vascular anastomoses in monochorionic placentas. Placenta. 2013;34(7):589-93.
73. Zoppi MA, Iuculano A, Monni G. Umbilical vein volume flow in monochorionic twin pairs at 11-14 weeks. J Perinat Med. 2014;42(4):515-21.
74. Khalil A, Beune I, Hecher K, Wynia K, Ganzevoort W, Reed K, et al. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. Ultrasound Obstet Gynecol. 2018:epub ahead of print.
75. Gordijn S, Beune I, Ganzevoort J, Khalil A, Thilaganathan B. Core outcomes for selective fetal growth restriction in twin pregnancies Liverpool: COMET; 2017 [Available from: http://www.comet-initiative.org/studies/details/998?result=true.
76. Leombroni M, Liberati M, Fanfani F, Pagani G, Familiari A, Buca D, et al. Diagnostic accuracy of ultrasound in predicting birth-weight discordance in twin pregnancy: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017;50:442-50.
77. D'Antonio F, Odibo A, Prefumo F, Khalil A, Buca D, Flacco M, et al. Weight discordance and perinatal mortality in twin pregnancies: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017:epub.
78. Neves A, Nunes F, Branco M, Almeida M, IS S. The role of ultrasound in the prediction of birth weight discordance in twin pregnancies: are we there yet? J Perinat Med. 2017:epub ahead of print.
79. TAMBA. A world first thanks to Tamba families 2017 [updated 6 July 2017. Available from: https://www.tamba.org.uk/blog/growth-charts.
80. Stagnati V, Zanardini C, Fichera A, Pagani G, Quintero RA, Bellocco R, et al. Early prediction of twin-to-twin transfusion syndrome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017;49(5):573-82.
81. D'Antonio F, Khalil A, Pagani G, Papageorghiou AT, Bhide A, Thilaganathan B. Crown–rump length discordance and adverse perinatal outcome in twin pregnancies: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2014;44(2):138-46.
82. Mackie F, Morris RK, Kilby MD. The prediction, diagnosis and management of complications in monochorionic twin pregnancies: The OMMIT (Optimal Management of Monochorionic Twins) study. BMC Pregnancy Childbirth. 2017;17(1):153.
83. Zoppi MA. NT and other ultrasound markers. Int J Gynecol Obstet. 2012;119:S260.

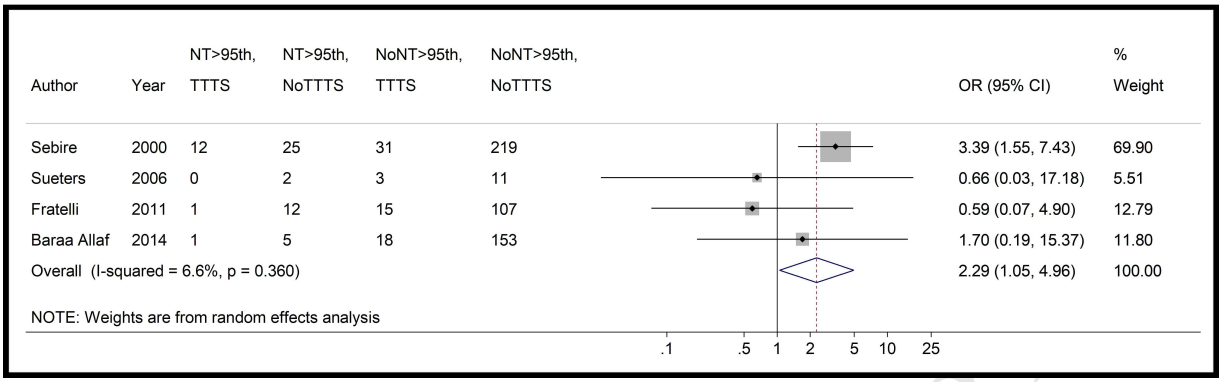
Table 1 Summary of accuracy of prognostic factors with a significant association with twin-twin transfusion syndrome

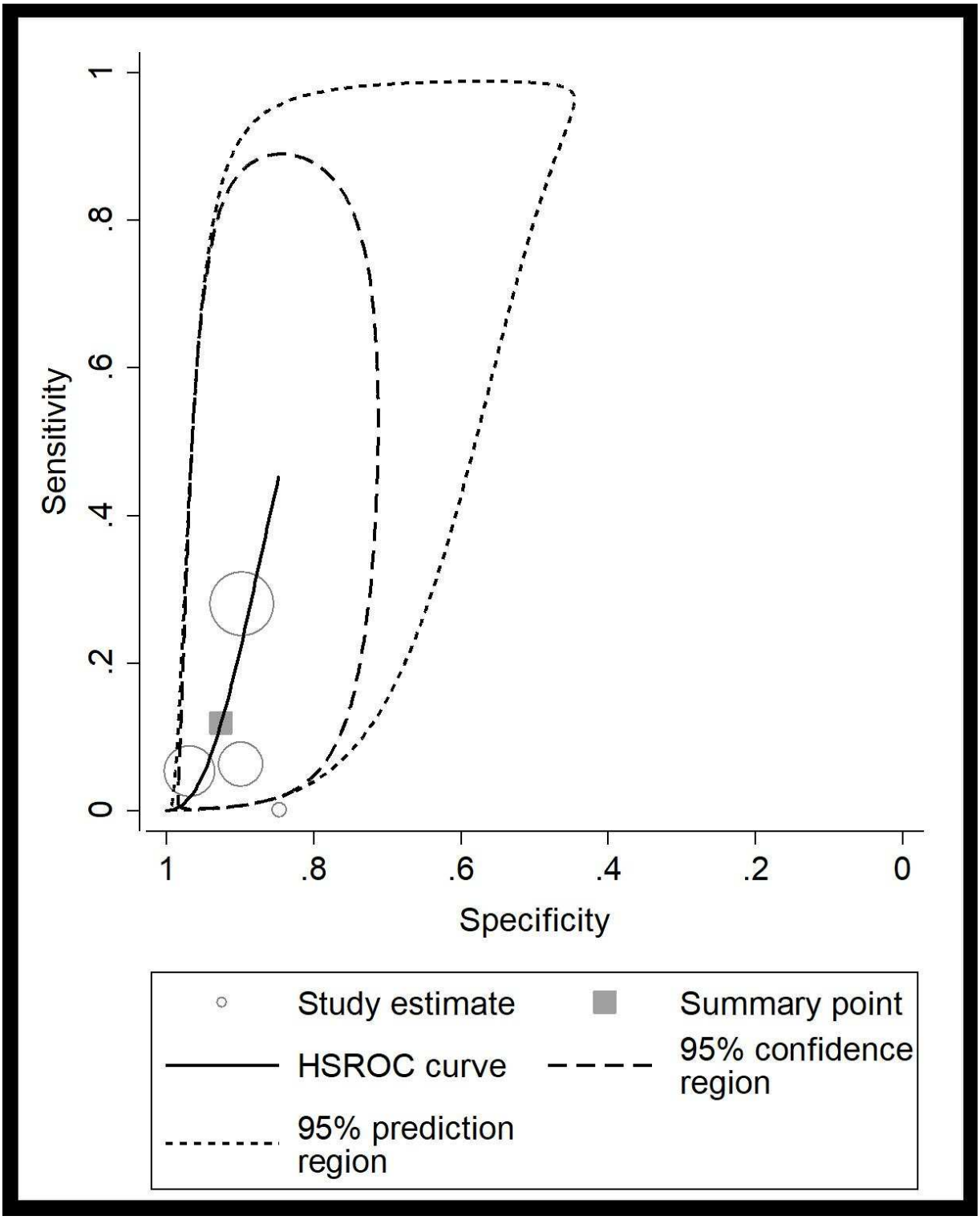
Prognostic factor	Sensitivity (95%CI)	Specificity (95%CI)	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)
NT>95th centile in one/both fetuses*	0.118 (0.035, 0.330)	0.926 (0.882, 0.954)	1.589 (0.589, 4.290)	0.953 (0.830, 1.094)
CRL discordance ≥10%†	0.203 (0.120, 0.308)	0.908 (0.882, 0.929)	2.180 (1.147, 4.142)	0.904 (0.794, 1.030)
Maternal ethnicity*	0.826 (0.672, 0.917)	0.278 (0.135, 0.917)	1.145 (0.941, 1.394)	0.624 (0.349, 1.117)

*Analysed by bivariate analysis. †Analysed by univariate analysis. CRL: crown-rump length, NT: nuchal translucency





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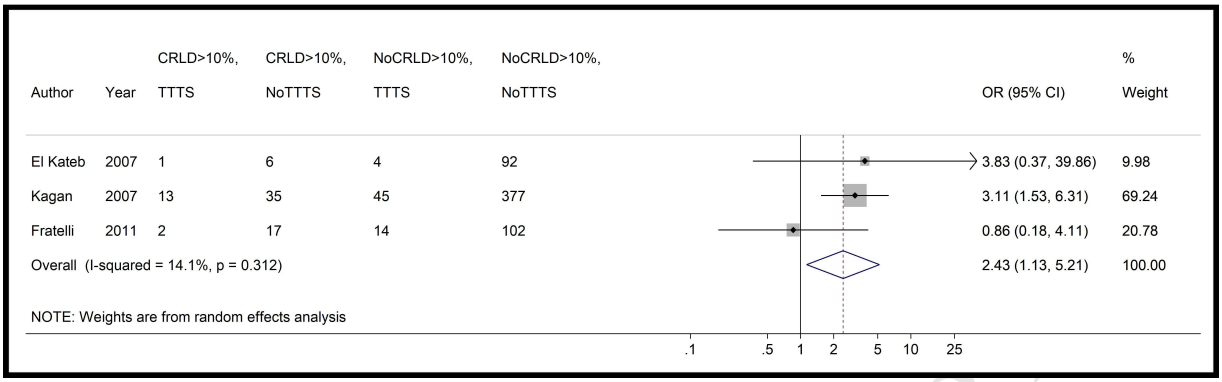

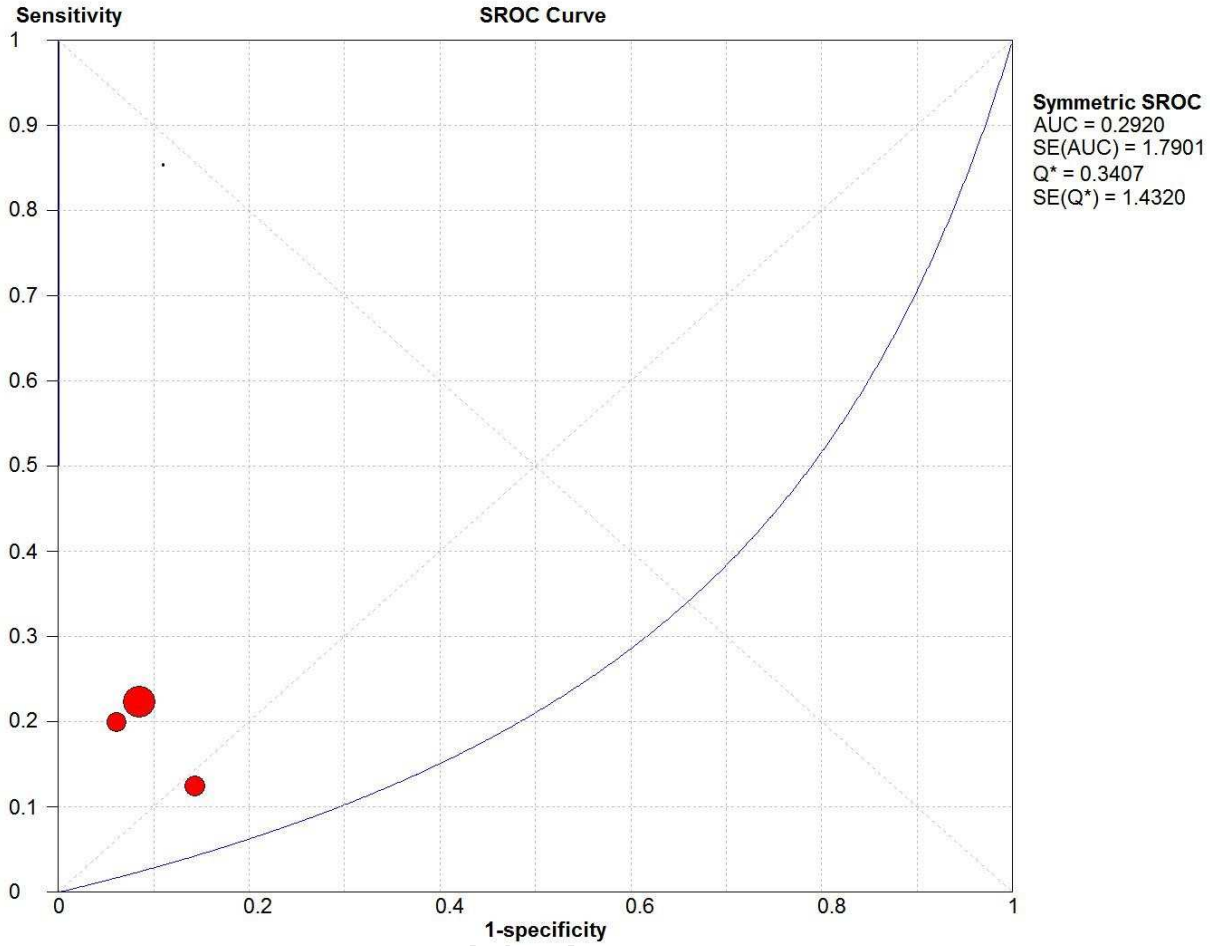

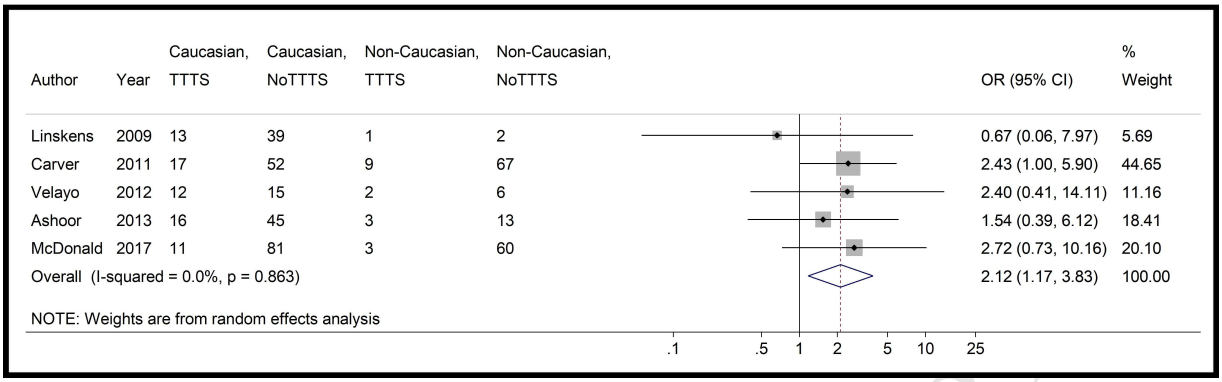

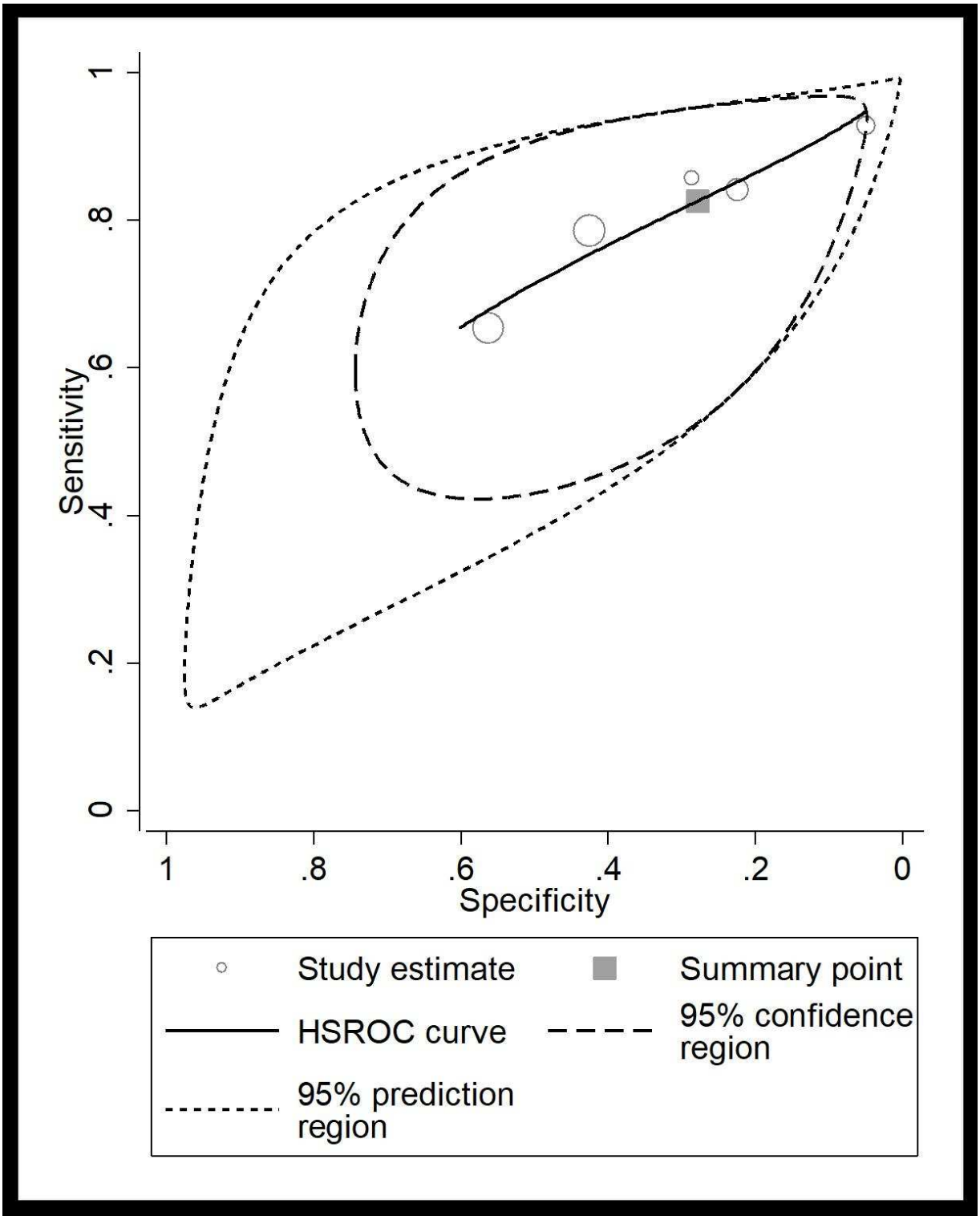
Sensitivity
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Specificity
Study estimate
Summary point
HSROC curve
95% confidence region
95% prediction region

Supplementary file Table 1 Characteristics of studies eligible for inclusion

Abbreviation: 1st T: 1st trimester, AC: abdominal circumference, AFI: amniotic fluid index, ART: assisted reproduction technology, AUC: area under (receiver operating characteristic) curve, β-hCG: beta-human chorionic gonadotropin, BMI: body mass index, BWD: birthweight discordance, C-section: Caesarean section, CRL: crown-rump length, DA: diamniotic, DC: dichorionic, DV: ductus venosus (Doppler), EFWD: estimated fetal weight discordance, FLA: fetoscopic laser ablation, GD: growth discordance, IUFD: intrauterine fetal demise, IUGR: intrauterine growth restriction, IVF: in vitro fertilisation, LBW: low birthweight, MA: monoamniotic, MC: monochorionic, MoM: multiple of median, NT: nuchal translucency, PAPP-A: pregnancy-associated plasma protein A, proBNP: prohormone of brain natriuretic peptide, sIUGR: selective intrauterine growth restriction, TAPS: twin anaemia-polycythaemia sequence, TOP: termination of pregnancy, TRAP: twin reversed arterial perfusion syndrome, TTTS: twin-twin transfusion syndrome, UAD: umbilical artery Doppler, USS: ultrasound scans, UVVF: umbilical venous volume flow A

*additional information/clarification obtained by contacting the authors

Author year	Study design, data collection, enrolment	Study population (Location, years, inclusion and exclusion criteria)	Total pregnancies eligible for study	Total MC pregnancies analysed in study	Outcomes used in review	Outcome definition used by study	Control group(s) definitions used by study	Potential prognostic factors
Ashoor 2013(26)	Case series, prospective, not stated	*Location:* ?1 centre in UK *Years:* 2006-2011 *INC:* twin pregnancies with live fetuses at 11-13 weeks 2 livebirths at ≥33 weeks, or severe TTTS necessitating FLA *EXC:* Maternal history of hypo/hyperparathyroidism or diabetes, fetal abnormalities, pre-eclampsia, BW<5th centile	Not stated	77	TTTS	'polyhydramnios surrounding the recipient fetus whose bladder was enlarged, oligo-/anhydramnios around the smaller donor fetus whose bladder was collapsed.'	Normal pregnancies with 2 livebirths at >33 weeks	Thyroid hormones, mode of conception (spontaneous or use of ovulation inducing drugs), maternal age (median), BMI (median), ethnicity
Bajoria 2006(27)	Unclear, not stated, not stated	*Location:* 1 centre in UK *Years:* not stated *INC:* MC pregnancies with/without discordant growth *EXC:* chronic TTTS, single/double IUFD, intrapartum stillbirth, aneuploidy, structural abnormalities, pregnancies	Not stated	32	BWD and sIUGR in same pregnancy	BWD ≥20% with no polyhydramnios in the larger twin, and smaller twin must have AC ≤5th centile with abnormal UAD, in same pregnancy	BWD ≤10% and normal amniotic fluid volume in both twins	Maternal age (median), ethnicity

		with: diabetes, hypertension, renal disease, cardiac disease						
Bajoria 2007(28)	Unclear, not stated, not stated	*Location:* ? centres in UK *Years:* not stated *INC:* MC pregnancies with/without TTTS *EXC:* single/double IUFD, intrapartum stillbirth, aneuploidy, structural abnormalities, pregnancies with: diabetes, hypertension, renal disease, cardiac disease	Not stated	30	TTTS	AFI ≥40cm in larger twin and ≤4cm in smaller twin. The smaller twin must also have IUGR, and the EFWD ≥15%, all in same pregnancy.	Concordant growth and AFI ≤24cm	Maternal age (median)
Baraa Allaf 2014(29)	Cohort, retrospective search of database with prospectively recorded data, consecutive enrolment to database and study	*Location:* 9 centres in USA *Years:* 2007-2011 *INC:* 2 live fetuses at 11-13^{+6} weeks *EXC:* chromosomal abnormalities, major congenital malformations, single/double IUFD in 1st T	Not stated	177	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS	NT >95th centile in one/both fetuses, NT discordance ≥20% (AUC), CRL discordance (AUC), combined NT and CRL discordance (AUC)
					IUGR	EFW<10th centile in either fetus	No IUGR	NT >95th centile in one/both fetuses
Ben-Ami 2016(30)	Cohort, not stated, not stated	*Location:* 7 centres in Israel, Spain, Germany and Canada *Years:* 1997-2013 *INC:* MCDA twin pregnancies undergoing NT scan at 11-14 weeks with 2 live fetuses *EXC:* fetal congenital/structural abnormalities, single/double IUFD, higher order multiple reductions, non-IVF fertility treatments	337	327	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS	Mode of conception (spontaneous or IVF/ICSI), maternal age (mean)
Carver 2011(31)	Cohort, retrospective collection of prospectively recorded data, consecutive	*Location:* 1 centre in USA *Years:* 2000-2009 *INC:* MCDA twins delivered at hospital and who underwent antenatal care at that hospital *EXC:* No sonographic examinations in 2nd T, no available antenatal records	151	145	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the	No TTTS	Maternal age (mean), ethnicity

						donor twin		
Chai 2013(32)	Cohort, retrospective, not stated	*Location:* 1 centre in China *Years:* 2005-2012 *INC:* MCDA pregnancies *EXC:* Aneuploidy/fetal anomalies, TTTS, TRAP, TAPS, LBW in both twins	Not stated	113	LBW	BW <10th centile in at least 1 twin	No LBW	Maternal age (mean)
Chang 2009(33)	Cohort, prospective, not stated	*Location:* 1 centre in Taiwan *Years:* 2006-2008 *INC:* live-born MCDA twins with a placenta able to be studied postnatally *EXC:* fetal anomalies, single IUFD, TTTS	53	51	sIUGR	EFW <10th percentile in 1 twin, with and without UAD abnormalities	No TTTS or sIUGR	Maternal age (mean)
Chang 2016(34)	Cohort, unclear, consecutive	*Location:* 1 centre in Taiwan *Years:* 2013-2015 *INC:* MC twins delivered by C-section with cord blood samples *EXC:* women who went into labour, TTTS, TAPS, congenital/structural or genetic malformations	Not stated	32	sIUGR	This is not clear. The terms sIUGR, fetal weight and BWD are used inter-changeably. Authors state: BWD >20% and BW <10th centile in 1 twin according to pregnancy birth weight chart, which is subdivided to those with and without UAD abnormalities	"Normal" MC twins, definition not stated	Fetal gender
Chang 2017(35)	Cohort, unclear, unclear	*Location:* 1 centre in Taiwan *Years:* 2013-2014 *INC:* MC twins delivered at centre with cord blood samples *EXC:* TTTS, congenital/structural or genetic malformations	Not stated	24	BWD and sIUGR in same pregnancy	EFW <10th centile and BWD >20% in same pregnancy	No sIUGR	Maternal age (mean), parity (mean)
Cosmi 2013(36)	Unclear, prospective, selected but unclear how	*Location:* 1 centre in Italy *Years:* 2009-2011 *INC:* MCDA pregnancies selected from previously	Not stated	12	sIUGR	EFW<10th centile in smaller twin, >10th centile larger twin, with	EFW >10th centile in both twins and confirmed after birth, and normal	Maternal age (median), parity

		published cohort but inclusion criteria not stated *EXC:* unknown last menstrual period, unknown chorionicity, triplets, TTTS or related conditions, MCMA, 1st T discrepancy in CRL>5 days, structural/chromosomal abnormalities, single IUFD, selective feticide, maternal history of cardiovascular disease, endocrine disorders, clinical chorioamnionitis, maternal consumption of: alcohol, drugs of abuse, nicotine				and without UAD abnormalities	UAD	
El Kateb 2007(37)	Cohort, prospective, consecutive	*Location:* 1 centre in France *Years:* 2002-2006 *INC:* MCDA pregnancies with 1st T NT and CRL measurements *EXC:* chromosomal abnormalities or congenital malformations	Not stated	103	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS	NT >95th centile (per fetus), CRL discordance ≥10% (per pregnancy)
					LBW	BW <5th percentile (per twin analysis)	No LBW	NT >95th centile (per fetus), CRL discordance ≥10% (per fetus)
Flöck 2013(38)	Cohort, retrospective search of database with prospectively recorded data, enrolment to database and study not stated	*Location: ?* centre in Germany *Years:* 2004-2010 *INC:* 'unaffected' twins on perinatal database *EXC:* structural fetal malformations, aneuploidy, vanishing twin, embryo reduction	849 fetuses (does not state how many pregnancies)	706 fetuses, equating to 353 pregnancies in total, 73/353 MCDA, 280 DCDA	sIUGR	Not stated	No sIUGR	Mode of conception (spontaneous or IVF/ICSI)
Fratelli 2011(39)	Cohort, retrospective, retrospective search of	*Location:* 1 centre in Italy *Years:* 2001-2009 *INC:* 1st T viable MC twin at 11-13+6 weeks and follow-up	136	135	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20	No TTTS	NT discordance ≥20%, NT >95th centile in one, NT >95th centile in both,

	database with prospectively recorded data, consecutive enrolment to database but unclear to study	at that centre *EXC:* pregnancies referred at later gestation, aneuploidy				weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin		NT >95th centile in one/both fetuses, NT discordance (median), NT discordance (AUC), CRL discordance ≥10%, CRL discordance (median), CRL discordance (AUC)
					sIUGR	EFW<10th percentile and abnormal UAD in same pregnancy	No sIUGR	NT discordance ≥20%, NT >95th centile in one, NT >95th centile in both, NT >95th centile in one/both fetuses, NT discordance (median), NT discordance (AUC), CRL discordance ≥10%, CRL discordance (median), CRL discordance (AUC)
					IUFD	Miscarriage <24 weeks or spontaneous death of at least 1 fetus	No IUFD	NT discordance ≥20%, NT >95th centile in one, NT >95th centile in both, NT >95th centile in one/both fetuses, NT discordance (median), CRL discordance ≥10%, CRL discordance (median)
Fujioka 2014(40)	Cohort, prospective, not stated	*Location:* 1 centre in Japan *Years:* 2007-2010 *INC:* MCDA twins with N-terminal proBNP levels measured at delivery *EXC:* congenital/chromosomal abnormalities, TTTS, referred to centre >26 weeks	124	73	sIUGR	EFW <10th percentile at 18-26 weeks	No sIUGR	Mode of conception (spontaneous or ART), fetal gender, maternal age (median)

Ghalili 2013(41)	Cohort, retrospective search of database with prospectively recorded data, consecutive enrolment to database and study	*Location*: 2 centres in Australia *Years:* 2006-2010 *INC:* MCDA twins undergoing 1st T scan, *EXC*: higher order multiples, pregnancies not conceived by IVF or spontaneously, non-viable or lethal structural anomalies at 12 week scan, unable to determine mode of conception or pregnancy outcome	312	294	LBW in one/ both twins	BW <10th centile in one/both twins	BW >10th centile in both twins	Mode of conception (spontaneous or IVF)
					TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS	Mode of conception (spontaneous or IVF)
Johansen 2014(42)	Cohort, retrospective search of database with prospectively recorded data, enrolment to database and study unclear	*Location:* 14 centres in Denmark *Years:* 2004-2006 *INC:* 2 live DA fetuses and chorionicity determined in 1st T *EXC:* unknown chorionicity, MCMA, reduction from higher order multiple, selective feticide or termination due to severe malformation/ chromosomal anomaly	281	260	BWD	BWD ≥20%	BWD <20%	CRL discordance ≥10%, CRL discordance ≥4% (OR), CRL discordance ≥5.5% (OR), CRL discordance ≥7% (OR), CRL discordance ≥10% (OR)
					Fetal loss of at least 1 fetus	Miscarriage ≤23+6 weeks, IUFD >23+6 weeks	2 livebirths	CRL discordance ≥10%, CRL discordance ≥10% (AUC), CRL discordance ≥4% (OR), CRL discordance ≥5.5% (OR), CRL discordance ≥7% (OR), CRL discordance ≥10% (OR)

Kagan 2007(43)	Cohort, retrospective search of database with prospectively recorded data, enrolment to database and study unclear	*Location:* 1 centre in UK *Years:* 2001-2006 *INC:* MCDA pregnancies undergoing combined 1st T aneuploidy screening *EXC:* chromosomal or structural defects, pregnancies with missing outcome data	560	470	TTTS	Severe TTTS requiring FLA. TTTS defined as: polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS	NT discordance ≥20%, NT discordance (median), NT discordance (AUC), CRL discordance ≥10%, CRL discordance (median), CRL and NT discordance (AUC)
					IUFD ('early')	Single/double IUFD at 13-18 weeks with no intervention	Not clear	NT discordance (AUC), CRL and NT discordance (AUC)
Kusanovic 2008(44)	Case-control, database with prospectively recorded data, enrolment to database and study unclear	*Location:* ? centres in USA and China *Years:* not stated *INC:* MCDA twin pregnancies 16-26 weeks *EXC:* pre-eclampsia at time of venepuncture, fetal congenital anomalies	Not stated	69	TTTS	Polyhydramnios (DVP ≥8cm) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS	Maternal age (median), gravida, height (median), weight (median), BMI (median), smoking
Lewi 2008a(45)	Cohort, prospective, not stated	*Location:* 2 centres in Belgium and Germany *Years:* 2004-2007 *INC:* MCDA twin pregnancies *EXC:* TTTS, spontaneous miscarriage, IUFD <16 weeks, structural anomalies that influence biometry	208	163	GD ('late' onset)	BWD ≥25% but EFWD<20% at 20 weeks	BWD <25%	CRL difference (mean)

Lewi 2008b(46)	Cohort, prospective, not stated	*Location:* 2 centre in Belgium and Germany *Years:* 2002-2007 *INC:* MCDA twin pregnancies with 2 live fetuses at 11-14 weeks *EXC:* single/double IUFD, TRAP, structural anomalies	202	200	TTTS	polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS	CRL discordance ≥6mm
Linskens 2009(47)	Cohort, retrospective search of database with prospectively recorded data, consecutive enrolment to database and study	*Location:* 1 centre in Netherlands *Years:* 2004-2008 *INC:* MCDA twins undergoing combined 1st T aneuploidy screening and followed up *EXC:* single/ double IUFD, preterm birth	61	55	TTTS	polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS and birth >26 weeks	NT discordance ≥20%, NT discordance ≥3.5mm, NT discordance (median), NT discordance (AUC), CRL discordance (median), maternal age (median), ethnicity, smoking, parity, mode of conception (spontaneous or ART)
Linskens 2010(48)	Cohort, retrospective search of database with prospectively recorded data, consecutive enrolment to database and study	*Location:* 1 centre in Netherlands *Years:* 2004-2009 *INC:* MCDA twins undergoing combined 1st T aneuploidy screening and followed up *EXC:* not stated	56	51	TTTS	polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS or single or double IUFD	PAPP-A (median MoM), β-hCG (median MoM)
Maiz 2009(49)	Cohort, prospective, unclear enrolment	*Location:* 1 centre in UK *Years:* 2006-2008 *INC:* MCDA and DCDA twin pregnancies with 2 live fetuses at 11-13^{+6} weeks *EXC:* unable to measure DV in both fetuses, outcome data missing	733 MCDA and DCDA (does not state number	179 (MCDA but we exclude 4 from analysis with aneuploidy /major	Severe TTTS	Severe TTTS requiring FLA or in which the fetus(es) died prior to FLA: 'ultrasound diagnosis of hydramnios in one	No TTTS or aneuploidy/major fetal defects	DV abnormal in one, DV abnormal in both, DV abnormal in one/both fetuses

			of MCDA)	defects, therefore 175)		twin and anhydramnios in the other, and absent or reversed end diastolic flow in either the umbilical artery or ductus venosus in one or both fetuses'		
					sIUGR	Severe sIUGR requiring FLA, definition of sIUGR not stated	No sIUGR or aneuploidy/major fetal defects	DV abnormal in one, DV abnormal in both, DV abnormal in one/both fetuses
					Single IUFD or miscarriage	Gestation at IUFD not stated but must be >14 weeks	No single IUFD or aneuploidy/major fetal defects	DV abnormal in one, DV abnormal in both, DV abnormal in one/both fetuses
Matias 2005(50)	Cohort, prospective, not stated	*Location:* 1 centre in Portugal *Years:* not stated *INC:* MCDA pregnancies referred to unit for 'routine 1st T ultrasonographic assessment' *EXC:* not stated	Not stated	50	TTTS	Anhydramnios and nonvisible bladder in the donor in combination with polyhydramnios and dilated bladder in the recipient.	No TTTS, 2 livebirths	Raw NT values, NT discordance ≥20%, DV abnormal in one, DV abnormal in both, DV abnormal in one/both fetuses, maternal age (median)
Matias 2010(51)	Cohort, prospective, not stated	*Location:* 1 centre in Portugal *Years:* 1997-2008 *INC:* MCDA pregnancies undergoing 1st T assessment *EXC:* malformations (e.g. megacystis), single IUFD	Not stated	99	TTTS	Oligohydramnios and non-visible bladder in the donor in combination with polyhydramnios and dilated bladder in the recipient	No TTTS	NT per fetus (mean), NT difference (mean), NT ratio (mean), NT difference (AUC), NT ratio (AUC), CRL per fetus (mean), CRL difference (mean), CRL ratio (mean), CRL difference (AUC), CRL ratio (mean), DV

								abnormal in one, DV abnormal in both, DV abnormal in one/both fetuses, DV abnormal (AUC)
Matias 2011(52)	Cohort, prospective, not stated	*Location:* 2 centres in Portugal and UK *Years:* 2006-2009 (UK), 1998-2009 (Portugal) *INC:* MC pregnancies that did not require antenatal interventions, and resulted in 2 healthy livebirths *EXC:* major fetal abnormalities, single/double IUFD, FLA for TTTS or sIUGR	326	237	BWD	BWD ≥20%	BWD <20%	DV abnormal in one/both fetuses
***McDonald 2017(53)**	Case series, prospective, consecutive	*Location:*1 centre in Australia *Years:* 2011-2014 *INC:* All MCDA twins attending for antenatal care at centre *EXC:* patients referred to centre for FLA, but remainder of care elsewhere	162	156	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS or chromosomal/ structural anomalies (parity, ethnicity). No TTTS, sIUGR, IUFD, TAPS, chromosomal/structural anomalies (maternal age, BMI)	Maternal age (mean), BMI (mean), ethnicity, parity
					sIUGR	EFW ≤10th centile in one or both twins, and/or EFWD >20%	No sIUGR or chromosomal/ structural anomalies (parity, ethnicity). No TTTS, sIUGR, IUFD, TAPS, chromosomal/structural anomalies (maternal age, BMI)	Maternal age (mean), BMI (mean), ethnicity, parity

					Single or double IUFD	Gestation at IUFD not stated, but median 22.0 (IQR 20.1-30.0 weeks) thus presumed 2nd trimester	No IUFD or chromosomal/ structural anomalies	Maternal age (mean), BMI (mean), ethnicity, parity
Memmo 2012(55)	Cohort, retrospective search of database with prospectively recorded data, consecutive enrolment to database and study	*Location:* 1 centre in UK *Years:* 2000-2010 *INC:* MC pregnancies with 1st T CRL and NT measurements *EXC:* TTTS Stage 1 managed conservatively who did not undergo FLA, MCMA, aneuploidy, fetal structural anomalies, spontaneous pregnancy loss <16 weeks	279	242	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	2 healthy livebirths at >34 weeks with no TTTS or sIUGR for all outcomes except parity which was compared to no TTTS.	NT discordance (median), NT larger twin (median), NT smaller twin (median), CRL discordance (median), CRL larger twin (median), CRL smaller twin (median), CRL discordance (AUC), maternal age (median), parity
					sIUGR 'early'	1 twin EFW <10th centile, before 26 weeks gestation and no signs of TTTS	2 healthy livebirths at >34 weeks with no TTTS or sIUGR except parity which was compared to no sIUGR.	NT discordance (median), NT larger twin (median), NT smaller twin (median), CRL discordance (median), CRL larger twin (median), CRL smaller twin (median), CRL discordance (AUC), maternal age (median), parity
***Miura 2014(54)**	Cohort, not stated, not stated	*Location:* 1 centre in Japan *Years:* not stated *INC:* MC pregnancies who visited centre at 12-21 weeks *EXC:* not stated	Not stated	28	TTTS	Polyhydramnios (DVP ≥8cm) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS or chromosomal/ structural anomalies	Maternal age (mean), parity
Moriichi 2013(56)	Cohort, prospective, not stated	*Location:* 1 centre in Japan *Years:* 2007-2011 *INC:* MC pregnancies with 2	Not stated	36	BWD	BWD ≥20%	BWD <20%	Maternal age (mean), parity

		livebirths *EXC:* chromosomal aberrations, congenital anomalies, IUFD, TTTS						
Murakami 2011(57)	Cohort, retrospective search of database with prospectively recorded data, consecutive enrolment to database and study	*Location:* 1 centre in Japan *Years:* 2006-2010 *INC:* Twins pregnancies attending for antenatal care at centre *EXC:* congenital anomalies associated with IUGR, multifetal pregnancy reduction	125 (51 MCDA, 74 DCDA)	42	TTTS	Polyhydramnios (DVP ≥8cm) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS	Mode of conception (spontaneous or IVF/ovulation induction)
					IUFD	Single/double IUFD >16 weeks	No IUFD	Mode of conception (spontaneous or IVF/ovulation induction)
***Sarais 2015(58)**	Cohort, retrospective search of database with prospectively recorded data, enrolment to database and study unclear	*Location:* 1 centre in Italy *Years:* 2007-2011 *INC:* MC pregnancies undergoing antenatal care at centre, which progressed >16 weeks *EXC:* higher order multiples, those presenting >16 weeks	Not stated	145	TTTS	Not stated	No TTTS or chromosomal/ structural anomalies	Mode of conception (spontaneous or IVF)
					IUFD	Single and double IUFD, >16 weeks	No IUFD or chromosomal/ structural anomalies	Mode of conception (spontaneous or IVF)
Schrey 2013(59)	Cohort, not stated, not stated	*Location:* ? centres in Canada *Years:* not stated *INC:* 'potential discordant MC twin pregnancies as candidates for placental sampling were identified in the antenatal period' *EXC:* fetal abnormalities, syndromes or infections, pre-eclampsia, diabetes, placental tumours	Not stated	15	BWD	BWD ≥20%	BWD <20% (all smaller twins also below the 10th centile)	Fetal gender
Sebire 2000(60)	Cohort, retrospective search of database with prospectively recorded data, consecutive enrolment to database	*Location: ?* centre in UK *Years:* unclear start date but delivered prior to June 1999 *INC:* MCDA pregnancies with 2 live fetuses at 10-14 weeks gestation, with outcome information available *EXC:* structural/chromosomal anomalies, TOP	303	287	Severe TTTS	Anhydramnios and no-visible bladder in the donor fetus in combination with polyhydramnios and a dilated bladder in the recipient fetus,	No TTTS	NT >95th centile per fetus, NT >95th centile in one/both fetuses

	unclear, but consecutive to study					which resulted in either miscarriage or fetal death or required intrauterine treatment or post-mortem evidence that the cause of death was TTTS.		
Sooranna 2001(61)	Unclear, prospective, not stated	*Location:* ? centres in UK *Years:* not stated *INC:* MC and DCDA pregnancies *EXC:* chronic TTTS, single IUFD, structural/chromosomal abnormalities, selective feticide, embryo reduction, maternal complications: hypertension, pre-eclampsia, renal/cardiac disease	Not stated	29	sIUGR	EFWD ≥20% with smaller twin's AC ≤5th centile and abnormal UAD in same pregnancy, with absence of polyhydramnios in the larger twin's sac	EFWD ≤10% and normal AFI throughout pregnancy	Fetal gender
Stagnati 2016(62)	Cohort, retrospective search of database with prospectively recorded data, consecutive enrolment to database and study	*Location:* 1 centre in Italy *Years:* 2008-2013 *INC:* MCDA pregnancies of with 1st T scan and antenatal care at centre *EXC:* referral after 1st T and/or incomplete follow-up, fetal structural abnormalities or abnormal karyotype, TTTS, TAPS, sIUGR or EFWD ≥25% at <28 weeks	172	136	sIUGR	EFW <5th centile	No sIUGR	Maternal age (median), BMI (median), mode of conception (spontaneous or ART), parity
					BWD	BWD >25%	BWD ≤25%	Maternal age (median), BMI (median), mode of conception (spontaneous or ART), parity
Sueters 2006(63)	Cohort, prospective, consecutive	*Location:* 1 centre in Netherlands *Years:* 2002-2004 *INC:* MCDA pregnancies, <16 weeks at referral, no signs of TTTS at initial USS *EXC:* fetal abnormalities	25	23	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS	NT >95th centile in one/both fetuses, maternal age (median), parity (median)
Sun 2017(64)	Case-control, retrospective,	*Location:* 1 centre in China *Years:* not stated	Not stated	14	BWD	BWD >20%	BWD <10% and normal UAD	Maternal age (mean), fetal gender

	not stated	*INC:* MCDA twins *EXC:* pre-eclampsia, TTTS, TAPS, fetal structural/chromosomal anomalies, maternal or pregnancy complications						
Tai 2007(65)	Cohort, prospective, not stated	*Location:* 1 centre in USA *Years:* 2000-2006 *INC:* twin pregnancies undergoing 1st T aneuploidy screening with 2 fetal heartbeats detected *EXC:* chromosomal/major congenital anomalies, 1st/2nd T TOP, MCMA	Not stated	43	TTTS	Not stated	No TTTS	CRL discordance ≥11%
Taylor-Clarke 2013(66)	Case-control, prospective, consecutive	*Location:* 1 centre in UK *Years:* not stated *INC:* MCDA pregnancies referred for ultrasound assessment from local maternity units *EXC:* not stated	Not stated	55	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS	Maternal age (median)
Torres-Torres 2010(67)	Cohort, retrospective, consecutive	*Location:* 1 centre in Mexico *Years:* 2008-2009 *INC:* MCDA twins undergoing antenatal care at centre *EXC:* not stated	Not stated	34 (but we excluded 4 from analysis with aneuploidy /major defects, therefore 30)	TTTS	Polyhydramnios (DVP ≥8cm) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	'Normal' with no complications, structural abnormalities, TTTS or sIUGR	Maternal age (median)
					sIUGR	EFW >10th centile in one fetus	'Normal' with no complications, structural abnormalities, TTTS or sIUGR	Maternal age (median)
***Velayo 2012(68)**	Case-control, retrospective, not stated	*Location:* ? centre in ? country *Years:* 2008-2009 *INC:* MCDA twins *EXC:* not stated	Not stated	35	TTTS	Polyhydramnios in 1 twin, oligohydramnios in the other twin. FLA performed for all TTTS patients	No TTTS or chromosomal/ structural anomalies. EFWD <15%, no polyhydramnios or oligohydramnios, UAD, MCA and	Maternal age (mean), BMI (mean), ethnicity, parity, mode of conception (spontaneous or not stated)

							DV Dopplers normal.	
Yinon 2014(69)	Cohort, prospective, not stated	*Location:* 1 centre in Israel *Years:* 2010-2012 *INC:* MCDA twins *EXC:* chronic hypertension, pre-gestational diabetes, congenital/chromosomal abnormalities, single IUFD at presentation	60	45	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	Normal: appropriately grown, EFWD <25%, normal amniotic fluid volumes, normal UADs, similar MCA-PSV in both twins for all outcomes, except smoking which is no TTTS.	Maternal age (median), gravida, BMI (median), smoking
				37	sIUGR	EFW <10th centile in one fetus and EFWD ≥25% in same pregnancy	Normal: appropriately grown, EFWD <25%, normal amniotic fluid volumes, normal UADs, similar MCA-PSV in both twins for all outcomes, except smoking which is no sIUGR	Maternal age (median), gravida, BMI (median), smoking
Zanardini 2014(70)	Cohort, prospective, not stated	*Location:* 1 centre in Italy *Years:* 2009-2012 *INC:* MCDA pregnancy attending centre for antenatal care *EXC:* MCMA, congenital cardiac anomaly/arrhythmia, fetal anomaly, TRAP, IUFD at presentation, maternal age <18 years, higher order multiples, patients lost to follow-up, TTTS diagnosed at <17 weeks	139	100	TTTS	Polyhydramnios (DVP ≥8cm before 20 weeks, or ≥10cm after 20 weeks) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	'Uncomplicated' throughout pregnancy, plus 4 with sIUGR (not defined)	Mode of conception (spontaneous or not stated), maternal age (median), parity

Zhang 2015(71)	Not stated, retrospective, not stated	*Location:* ? centres in China *Years:* 2009-2013 *INC:* MCDA twins *EXC:* severe maternal complications, TTTS, IUFD	Not stated	24	LBW	BW <10th centile in one twin	No LBW	Maternal age (mean), BMI (mean), fetal gender
***Zhao 2013(72)**	Cohort, retrospective, consecutive	*Location:* 1 centre in The Netherlands *Years:* 2002-2012 *INC:* MCDA twins with stored placentas *EXC:* TRAP, IUFD, higher order multiples, if underwent FLA or selective feticide	Not stated	235	TTTS	Polyhydramnios (DVP ≥8cm) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS or chromosomal/ structural anomalies	Fetal gender
					BWD	BWD ≥25%	No BWD or chromosomal/ structural anomalies	Fetal gender
					TAPS	Antenatally MCA-PSV >1.5 MoM in the donor and MCA-PSV <1.0 MoM in the recipient, and/or postnatally inter-twin haemoglobin difference >8.0 g/dl, and at least one of the following: reticulocyte count ratio >1.7 and placenta with only small (diameter < 1mm) vascular anastomoses	No TAPS or chromosomal/ structural anomalies	Fetal gender
Zoppi 2014(73)	Cohort, prospective, not stated	*Location:* ? centre in Italy *Years:* 2010-2012 *INC:* MCDA pregnancies 11-14 weeks gestation *EXC:* malformations, single or double IUFD <16 weeks, TOP <16 weeks	87	71	TTTS	Diagnosed <26 weeks. Polyhydramnios (DVP ≥8cm) in the recipient twin, oligohydramnios (DVP ≤2cm) in the donor twin	No TTTS, sIUGR, amniotic fluid discordance	UVVF larger twin (median), UVVF smaller twin (median), NT larger twin (median), NT smaller twin (median), CRL larger twin (median)

								CRL smaller twin (median)
				70	sIUGR	AC <5th centile in one fetus, and EFWD >25% in same pregnancy	?No TTTS, sIUGR, amniotic fluid discordance	UVVF larger twin (median), UVVF smaller twin (median), NT larger twin (median), NT smaller twin (median), CRL larger twin (median) CRL smaller twin (median)

Appendix A Search strategy

1. fetofetal blood transfusion or fetofetal transfusion or twin twin transfusion syndrome or twin to twin transfusion syndrome or twin-twin transfusion syndrome or twin-to-twin transfusion.mp.
2. twin anemia* polycythemia* sequence or TAPS.mp.
3. twin oligohydramnios-polyhydramnios sequence or TOPS.mp.
4. fetal death or intrauterine death or intrauterine demise or single twin demise or perinatal mortality or perinatal outcome* or neonatal mortality.mp.
5. small-for-gestational age or lbw or small for gestational age or sgr or small for date* or small for gestation* or fgr or iugr or intrauterine growth retard* or intrauterine growth restrict* or fetal growth retard* or fetal growth restrict* or growth restrict* or growth retard* or “Fetal growth retardation” or “Infant, Low Birth Weight” or low birth weight.mp.
6. Diseases in Twins/
7. amniotic fluid or amniotic fluid metabolism.mp.
8. placenta* or placental circulation or placental metabolism or placental blood supply or amnion or chorion.mp.
9. alpha-fetoprotein* or angiogenesis inducing agents or biological markers or chorionic gonadotropin, beta subunit or angiogenesis inducing agents or metabolomics* or vascular endothelial growth factor* or placental growth factor.mp.
10. neck/ultrasonography or nuchal translucency.mp. crown-rump length.mp. or biometry.mp or blood flow velocity.mp. or regional blood flow.mp. or umbilical arteries*.mp. or umbilical veins*.mp. or Doppler.mp. or ductus venosus.mp.

11. predictive value or tests* or risk assessment or risk factors* or prognostic* factors* or predictive* factors* or prognostic model or prognosis* or prediction* or predictor or formula or algorithm.mp.
12. twins*.mp.
13. monochorionic*.mp.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
15. 12 and 13 and 14

Appendix B Studies and potential prognostic factors not included in meta-analyses

Studies

In calculating discordance between ultrasound measures, all studies used the larger measure as the denominator, apart from Memmo et al.(55) who used the smaller NT as the denominator, however as they only reported the median NT discordance, there were too few studies to include this variable in meta-analysis. Chang et al.(33) could not be included in the analysis at all because they divided their AGR group into those with and without umbilical artery Doppler abnormalities and as the variable of maternal age was reported as a mean, the groups could not be combined. Cosmi et al.(36) was also not included in the maternal age analysis for the same reason as Chang et al., and Sun et al.(64) divided their control group into two sub-groups and thus could not be included in the maternal age analysis for the same reason. Velayo et al.(68) could not be included in this analysis because they did not report the standard deviations.

Flöck et al.(38) was not included in the TTTS outcome as the participants were also included in the larger cohort reported by Ben-Ami et al.(30). Zhao et al.(72) was not included in the TTTS analysis because they excluded those with TTTS who had undergone FLA and the group would have been heterogeneous. El Kateb et al.(37) could not be included in the PGR group because the variables and outcomes were only reported per fetus. The ‘early onset’ growth discordance group in the study by Lewi et al.(45) was not included as their definition of the outcome and variable both included difference in CRL. Kagan et al.(43) could not be included in the IUFD outcome because they only reported sufficient information for a 2x2 contingency

table on their sub-group of IUFD at 13-18 weeks. Nine studies were unable to be included in any meta-analysis due to an insufficient number of studies reporting the same variable and outcome(42, 45, 46, 48, 49, 51, 52, 65, 83) (results available from authors on request).

Potential prognostic factors

The following first trimester ultrasound measurements, maternal characteristics and serum biomarkers were reported for the outcomes under examination, but were unable to be included in meta-analysis (results available from authors on request).

Ultrasound measurements

The following factors were reported by less than 3 studies thus could not be included in meta-analysis: abnormal ductus venosus Doppler in one/both fetuses(49, 51); umbilical venous volume flow in fetus 1 ≥ fetus 2(73). NT discordance ≥10%, ≥30%, ≥40%, ≥50%(43); NT discordance >3.5 mm(47); NT difference(38, 51); NT ratio(51); NT larger twin(55, 73); NT smaller twin(55, 73); NT any twin(51). CRL discordance >4%, ≥5%, 5.5%, 7%, 10%, ≥15%, ≥20%(39, 42, 43); CRL discordance >11%(65); CRL discordance ≥6 mm, ≥12 mm(46); CRL difference(51); CRL ratio(51); CRL larger twin(55, 73); CRL smaller twin(55, 73); CRL any twin(51).

Maternal characteristics

Gravida (44, 69), height, and weight (44).

First trimester serum markers

Four first trimester maternal serum markers were investigated: β-hCG, PAPP-A, TSH and FT4, but meta-analysis was not possible. Linskens et al.(48) reported a trend in difference in β-hCG MoM in pregnancies with TTTS, and uncomplicated MC twins (median 1.99 vs 1.53 respectively, p=0.32, 51 pregnancies) and PAPP-A (median 1.94 vs 1.69 respectively, p=0.51, 51 pregnancies). Ashoor et al.(26) reported no

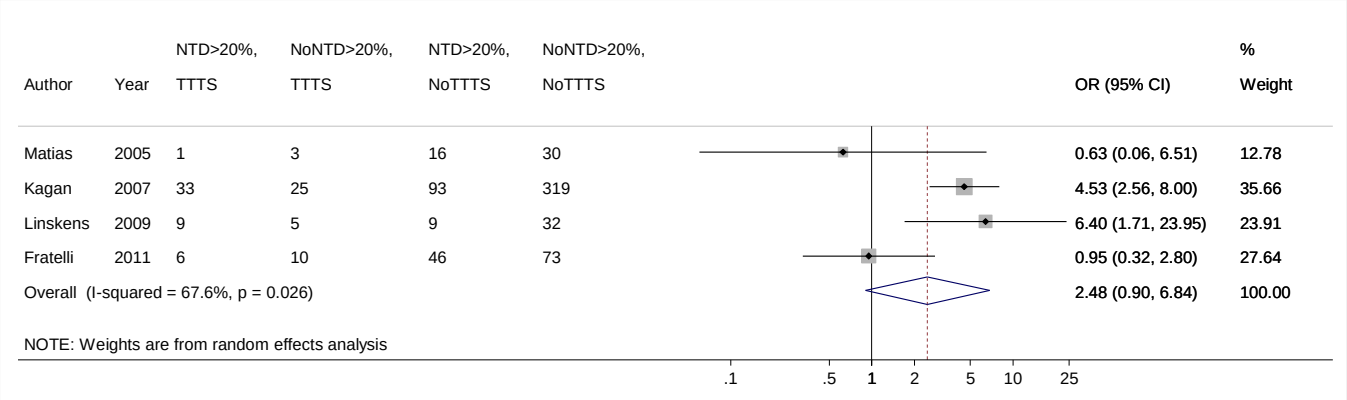
difference in TSH, FT4 or free β-hCG MoM in 17 pregnancies with TTTS and 'normal outcome twins', although the authors do not state if the control group included DC twins thus the number of MC twin pregnancies in the analysis is not clear. The following levels are reported in the TTTS and 'normal outcome twins' respectively: TSH (median 1.38 [IQR 0.52–2.05] vs 1.00 [IQR 0.26–1.36] respectively, p=0.424, number of pregnancies not clear), FT4 MoM (median 0.94 [IQR 0.90–1.16] vs 0.98 [IQR 0.91–1.08], p=0.773, number of pregnancies not clear), free β-hCG MoM (median 0.95 [IQR 0.51–2.22] vs 1.00 [IQR 0.69–1.36], p=0.997, number of pregnancies not clear). These serum markers were only reported in the context of TTTS, and not the other outcomes.

Appendix C Meta-analyses with no moderate/strong prognostic association

NT discordance ≥20% and TTTS

There was a trend towards a significant association between NT discordance ≥20% and TTTS, however there was a high-risk of heterogeneity (OR 2.48 [95%CI 0.90, 6.84] I^2=67.6%, 4 studies, 710 pregnancies) (Figure C.1). To investigate the heterogeneity a sensitivity analysis was performed removing Kagan et al.(43) as it only included those with severe TTTS requiring FLA in their group, whereas others included those with a diagnosis of TTTS irrespective of intervention. Removing Kagan et al. made no difference to the results or level of heterogeneity (results not shown) therefore this study was included. On visual inspection of the forest plot, Matias et al. was noted to be an outlier, however there was no reason to remove the study based on study design or characteristics, therefore this study was included.

Figure C.1 Forest plot of association between NT discordance ≥20% and TTTS



Maternal age and TTTS

No significant association between maternal age and TTTS was found (SMD 0.02 [95%CI -0.19, 0.24] I^2=54.9%, 15 studies, 1336 pregnancies) (Figure C.2). Although the I^2 suggests a high-risk of heterogeneity, there were no obvious outliers from visual inspection of the forest plot or in study design. The funnel plot (Figure C.3)

does appear asymmetrical, although Egger's test does not suggest small-study effects with p=0.576.

Figure C.2 Forest plot of association between maternal age and TTTS

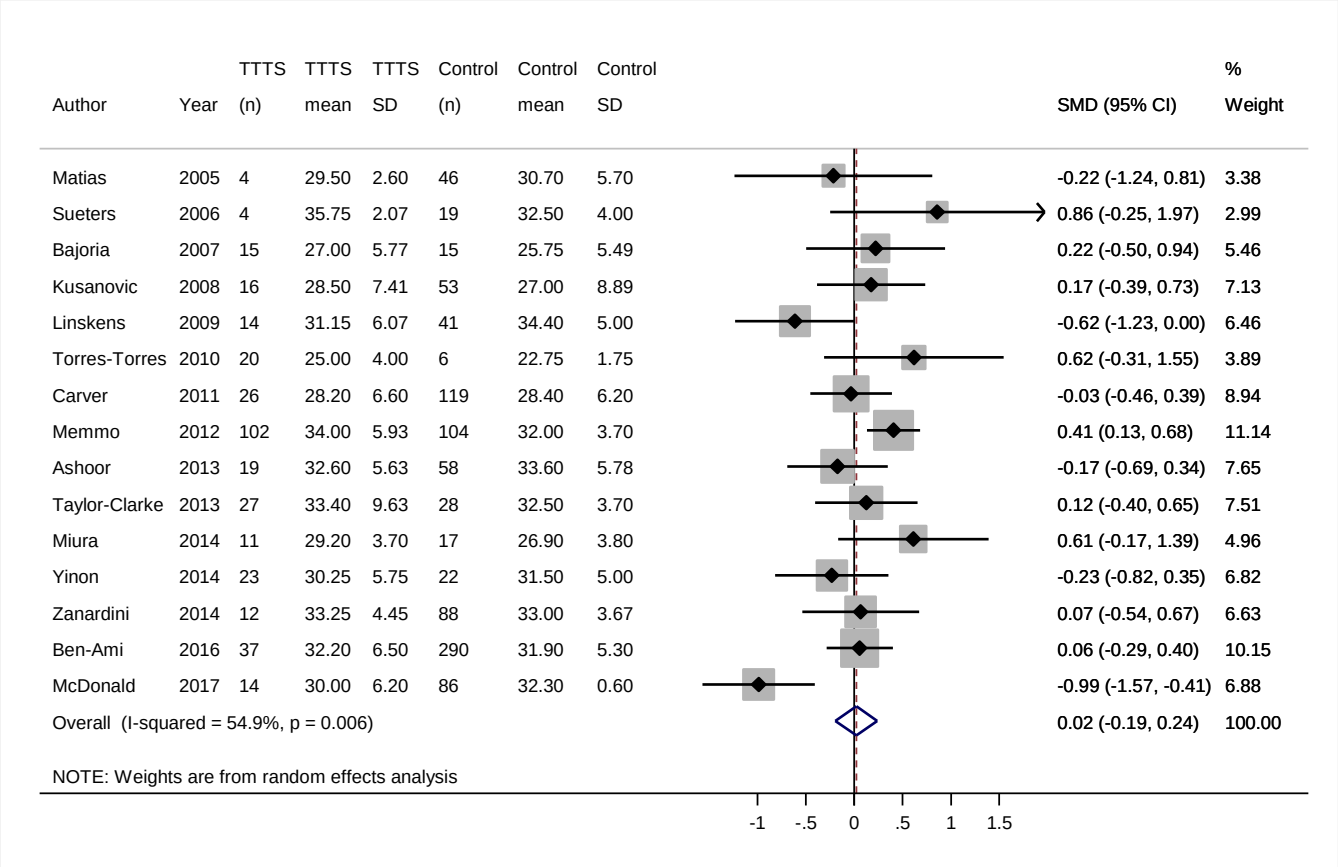
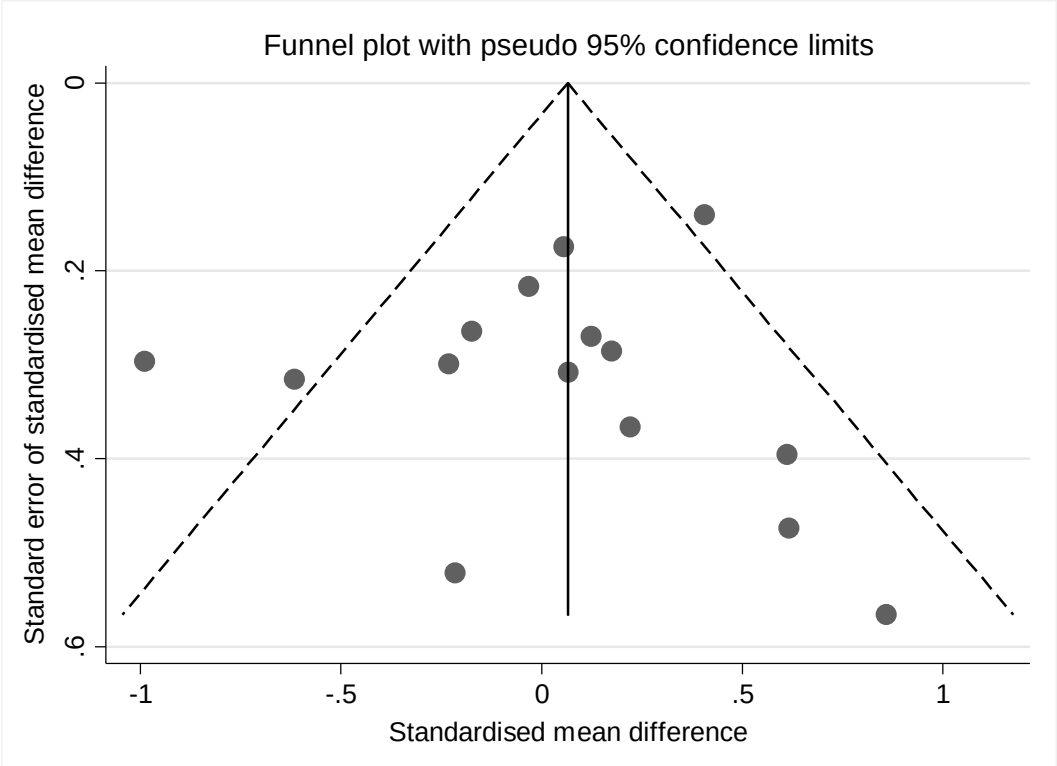


Figure C.3 Funnel plot of maternal age and TTTS studies

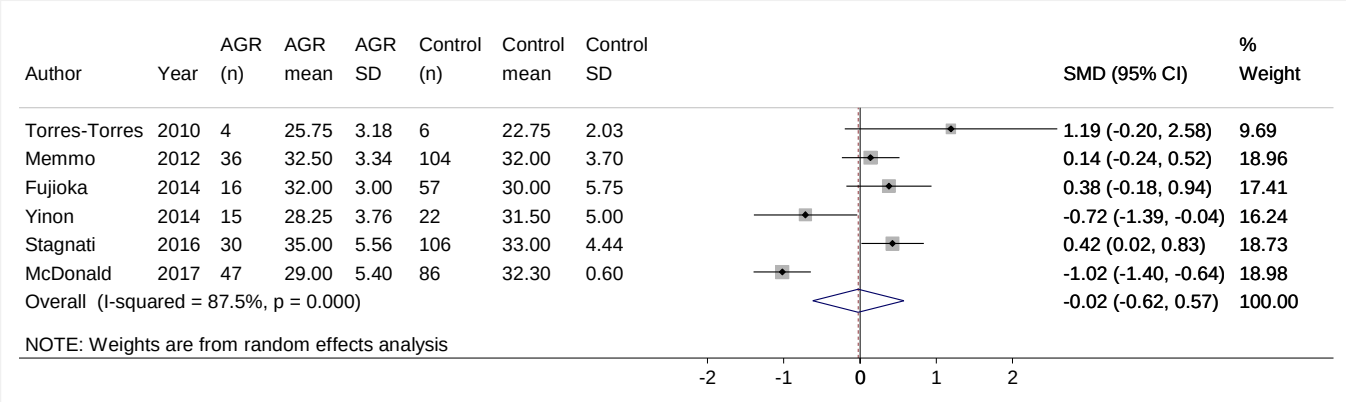


Maternal age and AGR

No significant association between maternal age and AGR was found (SMD -0.02 [95%CI -0.62, 0.57] I^2=87.5%, 6 studies, 529 pregnancies) (Figure C.4). To investigate the high-risk of heterogeneity, a sensitivity analysis was performed removing Memmo et al.(55), Fujioka et al.(40) and Stagnati et al.(62) as these studies restricted their definitions of AGR based on gestation. Removing these studies made no difference to the results or level of heterogeneity (results not shown) therefore the studies were included. An additional sensitivity analysis was performed by removing Yinon et al.(69) and McDonald et al.(53) following visual assessment of the forest plot. This decreased the I^2 to 0.0% and produced a significant association between maternal age and AGR (SMD 0.32 [05%CI 0.08, 0.56], 4 studies, 359 pregnancies) (forest plot not shown) although the effect of maternal age is small thus the prognostic ability was not further investigated. When

the studies were examined in more detail, these were the only 2 studies in the meta-analysis that included twins with estimated fetal weight discordance (EFWD) in their abnormal growth group, whereas the definition used in the other 4 studies required the EFW of 1 twin to be <10th centile(40, 55, 67) or 5th centile(62).

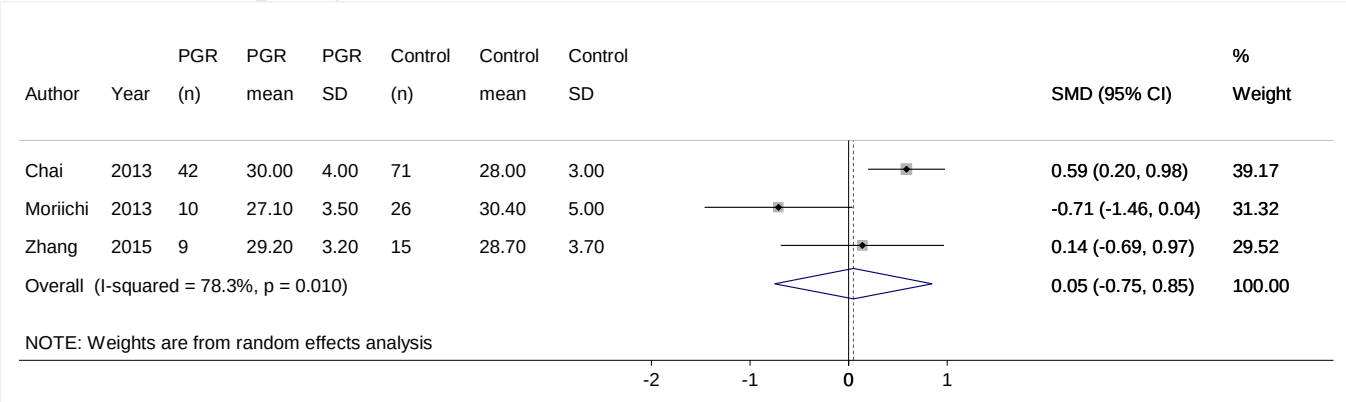
Figure C.4 Forest plot of association between maternal age and antenatal growth restriction (AGR)



Maternal age and PGR

No significant association between maternal age and PGR was found (SMD 0.05 [95%CI -0.75, 0.85] I^2=78.3%, 3 studies, 173 pregnancies) (Figure C.5). It was not possible to investigate the high-risk of heterogeneity as there were too few studies.

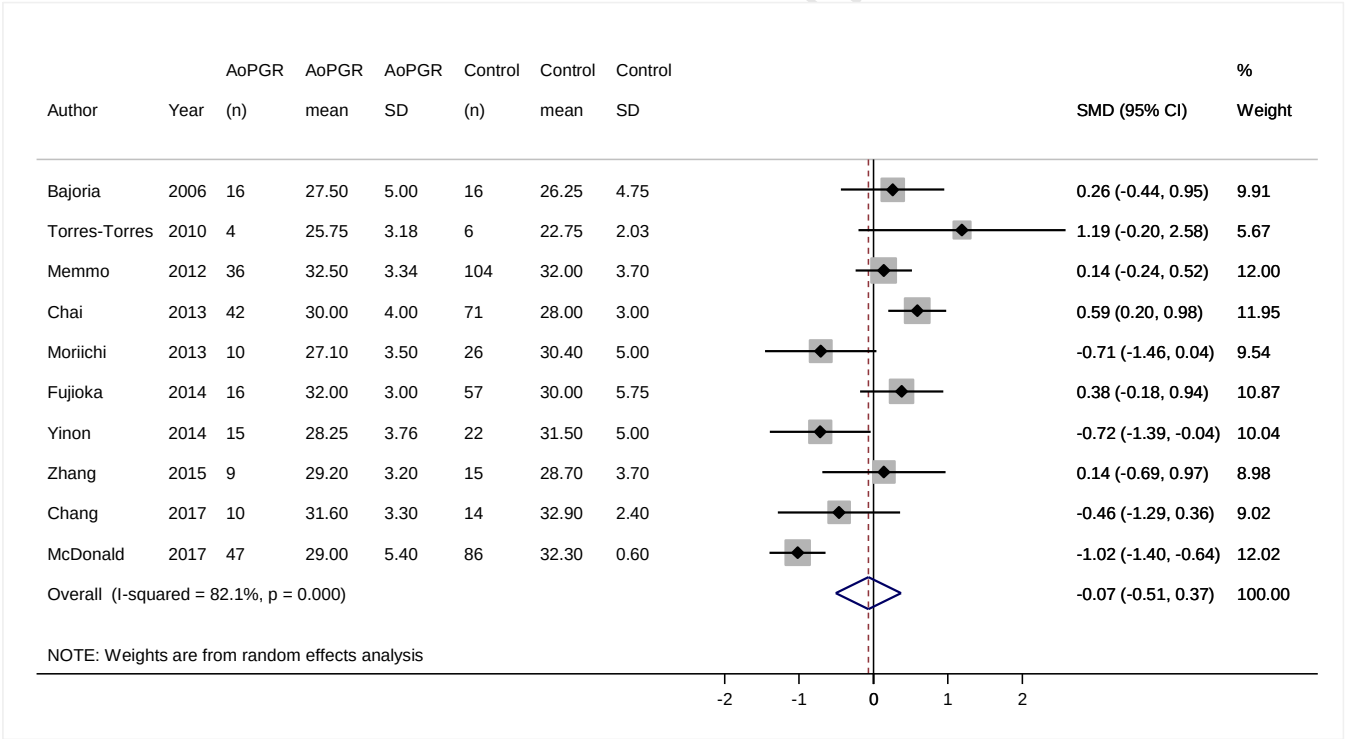
Figure C.5 Forest plot of association between maternal age and postnatal growth restriction (PGR)



Maternal age and AoPGR

No significant association between maternal age and AoPGR was found (SMD -0.07 [95%CI -0.51, 0.37] I^2=82.1%, 10 studies, 622 pregnancies) (Figure C.6). To investigate the high-risk of heterogeneity, a sensitivity analysis was performed removing Memmo et al.(55) and Fujioka et al.(40) as these studies restricted their definitions of AGR based on gestation. However, removing these studies made no difference to the results or level of heterogeneity (results not shown) therefore these studies were included.

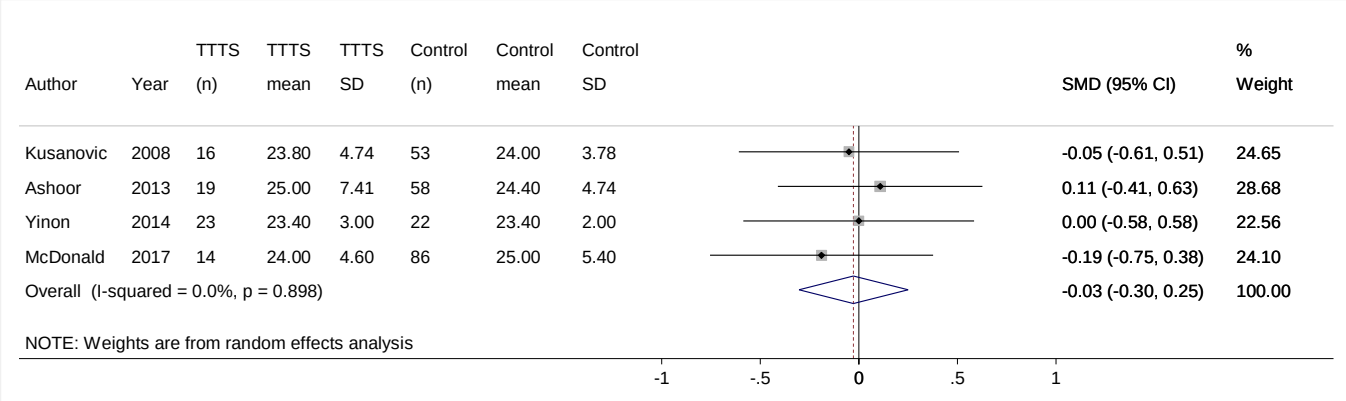
Figure C.6 Forest plot of association between maternal age and antenatal or postnatal growth restriction (AoPGR)



Maternal BMI and TTTS

No significant association between maternal BMI and TTTS was found (SMD -0.03 [95%CI -0.30, 0.25] I^2=0.0%, 4 studies, 291 pregnancies) (Figure C.7).

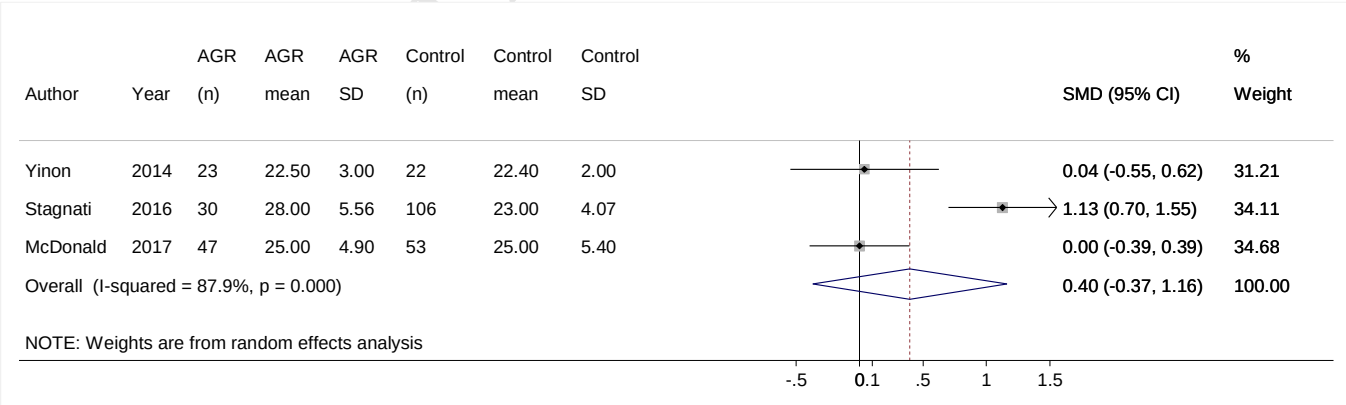
Figure C.7 Forest plot of association between maternal BMI and TTTS



Maternal BMI and AGR

No significant association between maternal BMI and AGR was found (SMD 0.40 [95%CI -0.37, 1.16] I^2=87.9%, 3 studies, 281 pregnancies) (Figure C.8). Following visual assessment of the forest plot, Stagnati(62) was noted to be an outlier, which was the only study in the meta-analysis that did not include EFWD in their definition of abnormal growth. It was not possible to investigate this further as there were too few studies.

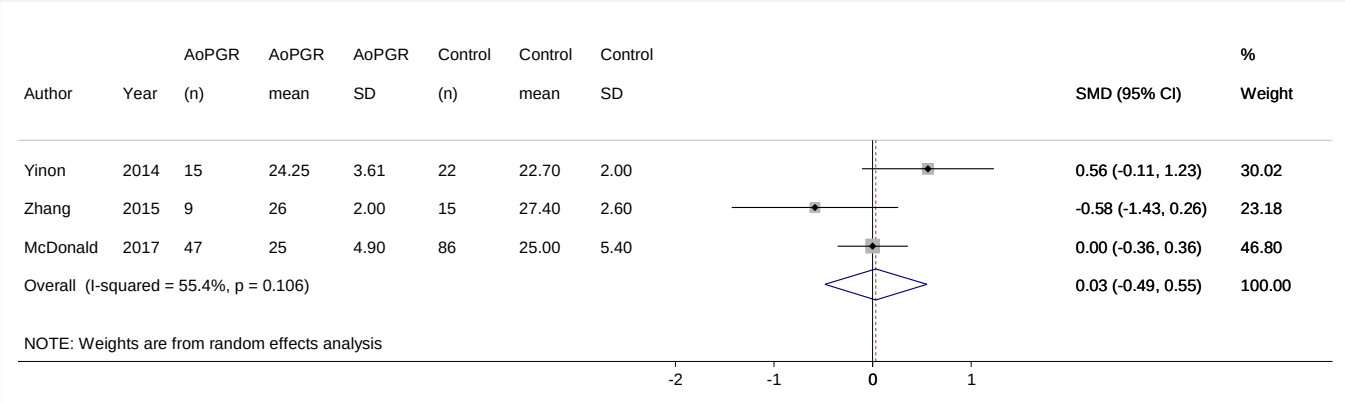
Figure C.8 Forest plot of association between maternal BMI and antenatal growth restriction (AGR)



Maternal BMI and AoPGR

No significant association between maternal BMI and AoPGR was found (SMD 0.03 [95%CI -0.49, 0.55] I^2=55.4%, 3 studies, 194 pregnancies) (Figure C.9). It was not possible to investigate the high-risk of heterogeneity as there were too few studies.

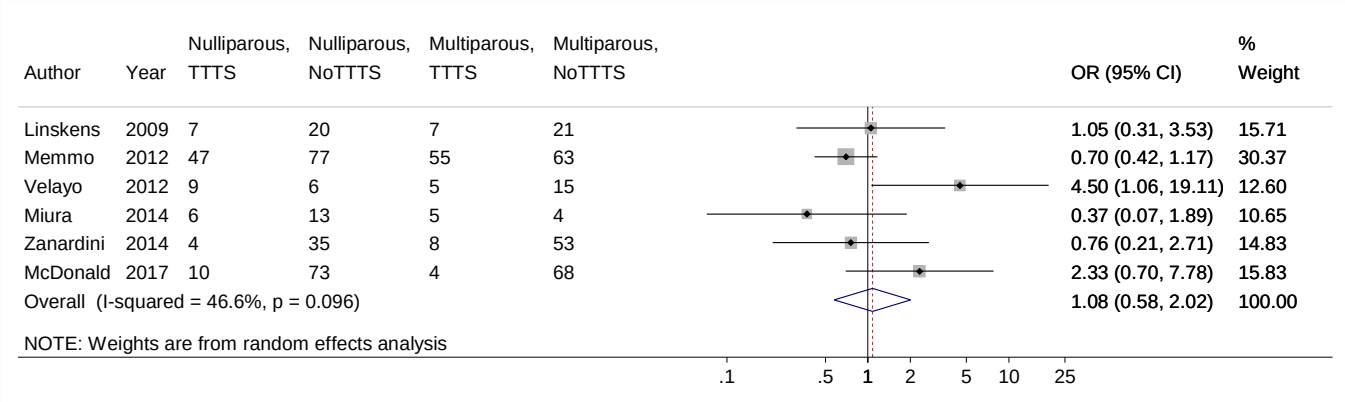
Figure C.9 Forest plot of association between maternal BMI and antenatal or postnatal growth restriction (AoPGR)



Parity and TTTS

An OR >1 indicated a higher-risk of TTTS if the woman was nulliparous, and an OR <1 indicated a higher-risk of TTTS if the woman was multiparous. No significant association between parity and TTTS was found (OR 1.08 [95%CI 0.58, 2.02] I^2=46.4%, 6 studies, 615 pregnancies) (Figure C.10).

Figure C.10 Forest plot of association between parity and TTTS

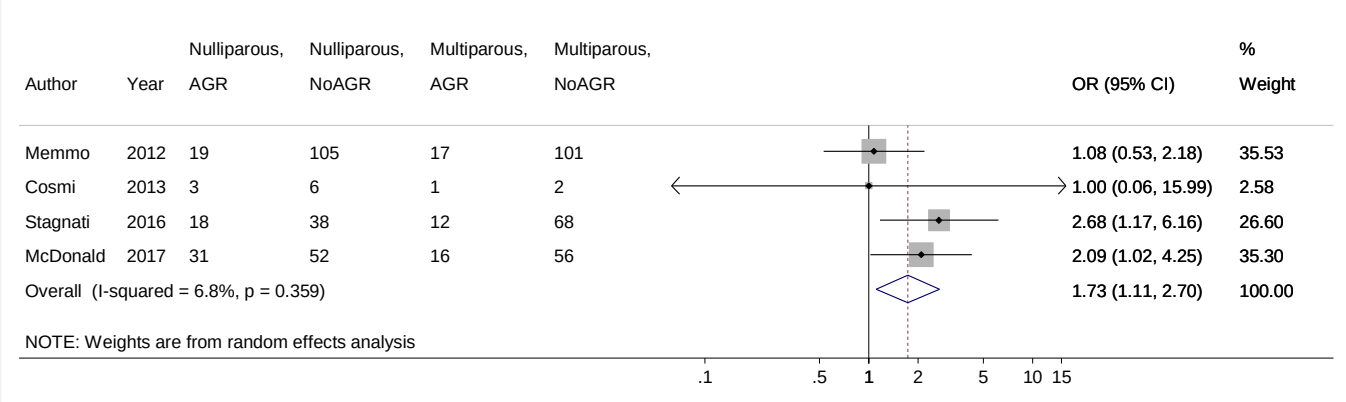


Parity and AGR

An OR >1 indicated a higher-risk of AGR if the woman was nulliparous, and an OR <1 indicated a higher-risk of AGR if the woman was multiparous. There appears to be an association between parity and AGR (OR 1.73 [95%CI 1.11, 2.70] I^2=6.8%, 4

studies, 545 pregnancies) (Figure C.11) although as it was a weak association with an OR <2 this was not further investigated.

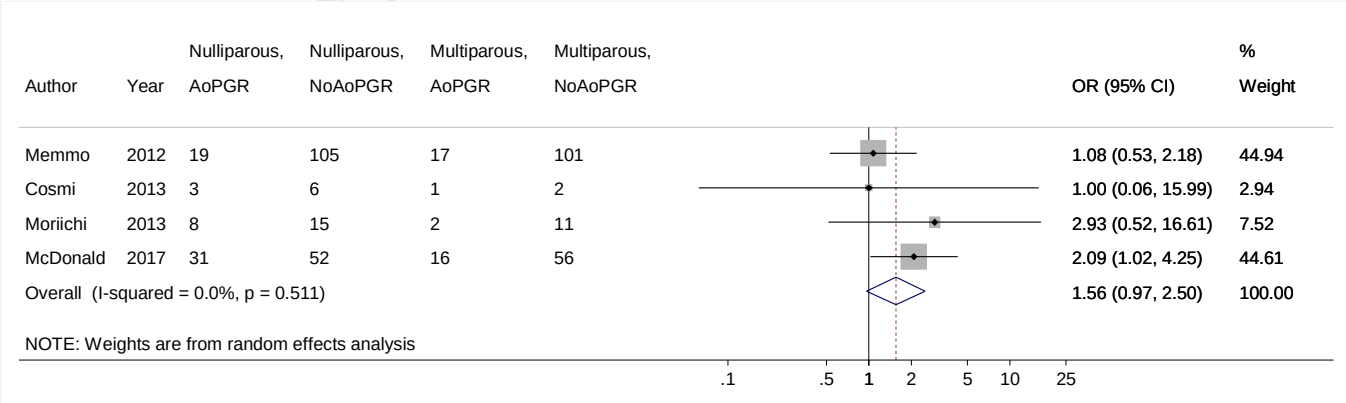
Figure C.11 Forest plot of association between parity and antenatal growth restriction (AGR)



Parity and AoPGR

An OR >1 indicated a higher-risk of AoPGR if the woman was nulliparous, and an OR <1 indicated a higher-risk of AoPGR if the woman was multiparous. A trend towards an association between parity and AoPGR was found (OR 1.56 [95%CI 0.97, 2.50], I^2=0.0%, 4 studies, 445 pregnancies) (Figure C.12).

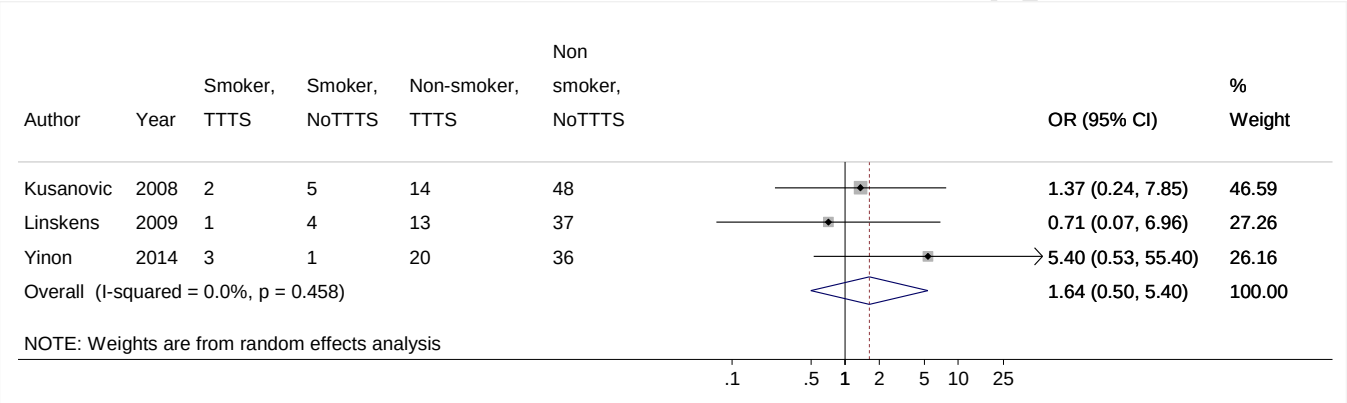
Figure C.12 Forest plot of association between parity and antenatal or postnatal growth restriction (AoPGR)



Maternal smoking and TTTS

An OR >1 indicated a higher-risk of TTTS if the woman was a smoker, and an OR <1 indicated a higher-risk of TTTS if the woman was a non-smoker. No significant association between maternal smoking and TTTS was found (OR 1.64 [95%CI 0.50, 5.40] I^2=0.0%, 3 studies, 184 pregnancies) (Figure C.13).

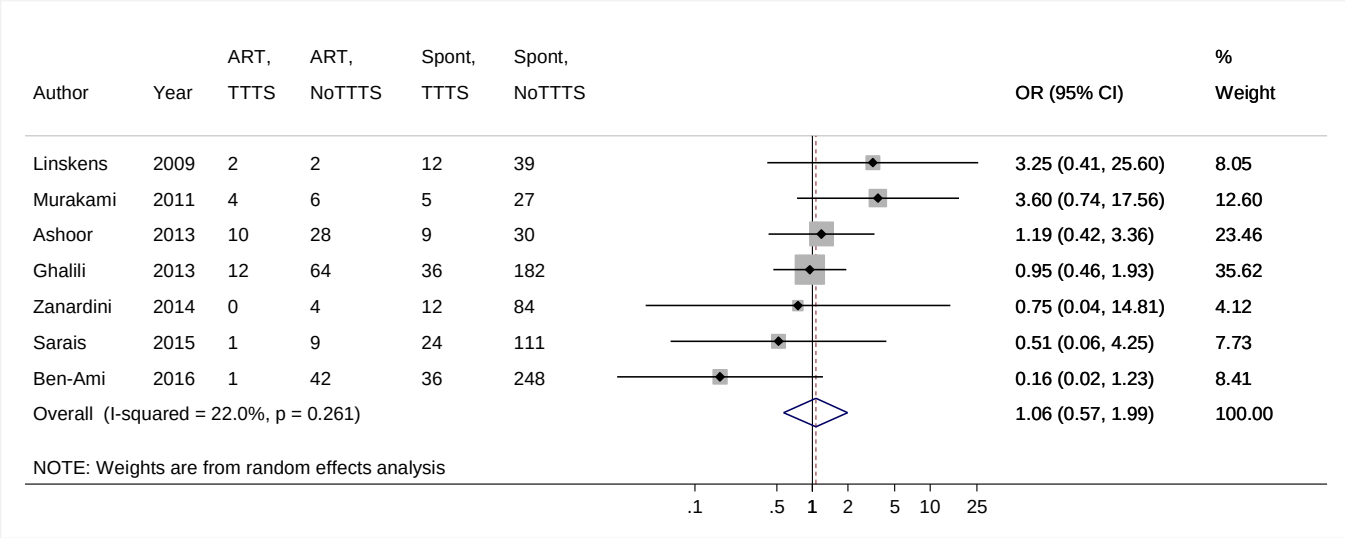
Figure C.13 Forest plot of association between maternal smoking and TTTS



Mode of conception and TTTS

An OR >1 indicated a higher-risk of TTTS if the pregnancy was conceived by ART, and an OR <1 indicated a higher-risk of TTTS if the pregnancy was conceived spontaneously. No significant association between mode of conception and TTTS was found (OR 1.06 [95%CI 0.57, 1.99] I^2=22.0%, 7 studies, 1040 pregnancies) (Figure C.14).

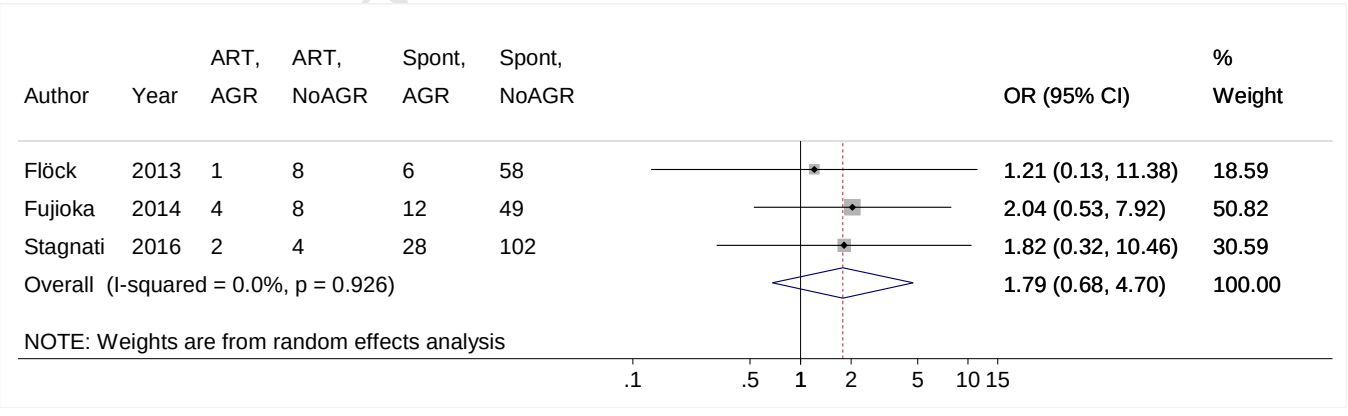
Figure C.14 Forest plot of association between mode of conception and TTTS



Mode of conception and AGR

An OR >1 indicated a higher-risk of AGR if the pregnancy was conceived by ART, and an OR <1 indicated a higher-risk of AGR if the pregnancy was conceived spontaneously. No significant association between mode of conception and AGR was found (OR 1.79 [95%CI 0.68, 4.70] I^2=0.0%, 3 studies, 282 pregnancies) (Figure C.15).

Figure C.15 Forest plot of association between mode of conception and antenatal growth restriction (AGR)

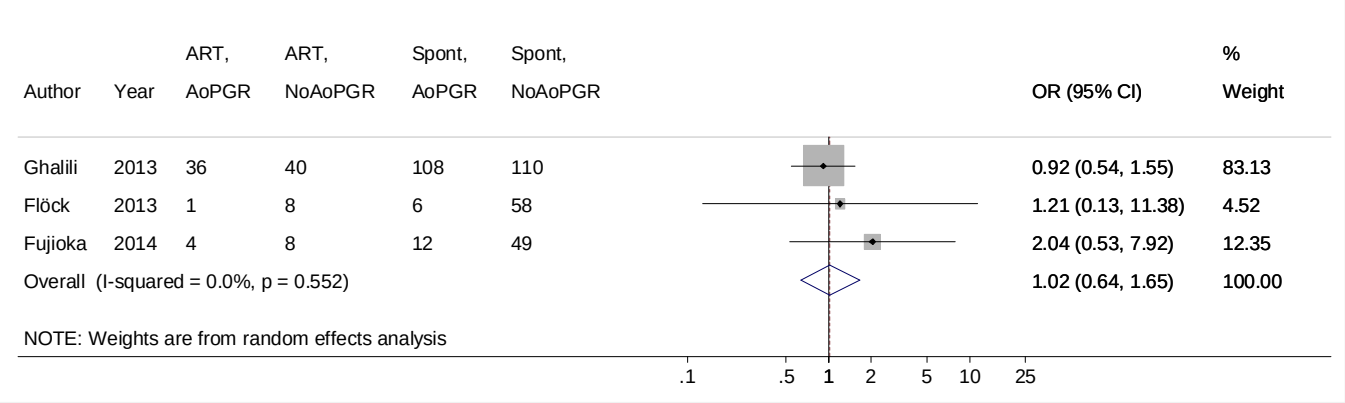


Mode of conception and AoPGR

An OR >1 indicated a higher-risk of AoPGR if the pregnancy was conceived by ART, and an OR <1 indicated a higher-risk of AoPGR if the pregnancy was conceived

spontaneously. As Ghalili et al.(41) presented both birthweight discordance and low birth weight in one baby, and in two babies, the latter two measures were combined to reflect low birthweight in at least one twin. No association between mode of conception and AoPGR was found (OR 1.02 [95%CI 0.64, 1.65], I^2=0.0%, 3 studies, 440 pregnancies) (Figure C.16).

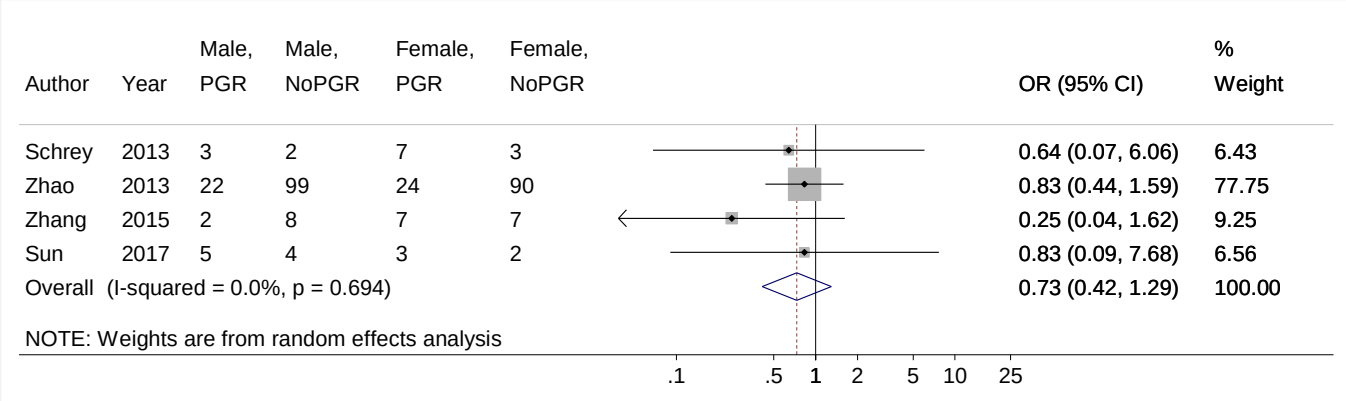
Figure C.16 Forest plot of association between mode of conception and antenatal or postnatal growth restriction (AoPGR)



Fetal gender and PGR

An OR >1 indicated a higher-risk of PGR if the fetuses were male, and an OR <1 indicated a higher-risk of PGR if the fetuses were female. No significant association between fetal gender and PGR was found (OR 0.73 [95%CI 0.42, 1.29] I^2=0.0%, 4 studies, 288 pregnancies) (Figure C.17). Investigation of unusual results with sensitivity analysis revealed no significant difference.

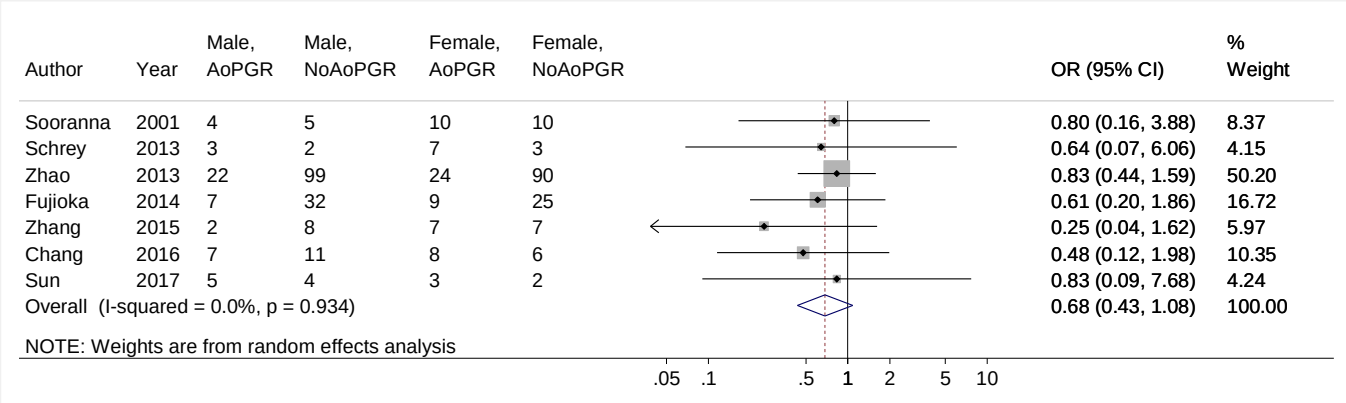
Figure C.17 Forest plot of association between fetal gender and postnatal growth restriction (PGR)



Fetal gender and AoPGR

An OR >1 indicated a higher-risk of AoPGR if the fetuses were male, and an OR <1 indicated a higher-risk of AoPGR if the fetuses were female. No significant association between fetal gender and AoPGR was found (OR 0.68 [95%CI 0.43, 1.08], I^2=0.0%, 7 studies, 422 pregnancies) (Figure C.18).

Figure C.18 Forest plot of association between fetal gender and antenatal or postnatal growth restriction (AoPGR)



Appendix D MOOSE Checklist

	Reported on page	Brief Description
Reporting of background should include		
Problem definition	4-5	Monochorionic twins are considered high-risk pregnancies. No prognostic test is currently available to predict which monochorionic twin pregnancies will develop twin-twin transfusion syndrome, intrauterine growth restriction, intrauterine fetal death, therefore these pregnancies are closely monitored antenatally which has an impact on patients, health care providers and resources.
Hypothesis/research question statement	5	To assess the ability of first trimester pregnancy related factors (ultrasound measurements, maternal characteristics, biomarkers) to predict complications in MC twin pregnancies.
Description of study outcomes	6-7	Twin-twin transfusion syndrome, antenatal growth restriction, postnatal growth restriction, single intrauterine fetal death, double intrauterine fetal death
Type of exposure or intervention used	6	First trimester ultrasound measurements, biomarkers and maternal characteristics
Type of study designs used	8	No limitation, but must be able to assess association between variable and outcome
Study population	5	Women with a monochorionic diamniotic twin pregnancy. Pregnancies affected by chromosomal/structural anomalies, monoamniotic twins, double fetal loss prior to 14 weeks gestation, or twin reversed arterial perfusion were excluded.
Reporting of search strategy should include		
Qualifications of searchers (eg librarians and investigators)	9	FLM MBChB, MRes MJH undergraduate medical student learning how to perform a systematic review and meta-analysis RKM MBChB, PhD, MRCOG MDK MBBS, DSc, MD, FRCOG
Search strategy, including time period used in the synthesis and key words	8 Appendix A	Keywords and MeSH terms relating to the following were used: TTTS, TAPS, TOPS, fetal death, IUGR, diseases in twins, amniotic fluid, placenta, biomarkers, ultrasonographic markers and prediction; and combined with “monochorionic” and “twins”. The date of publication was limited from inception to 12 May 2017.
Effort to include all available studies, including contact with authors	8 Acknowledgements	Effort was made to contact authors where appropriate
Databases and registries searched	7	Cochrane Library databases.
Search software used, name and	7	Medline, Web of Science, Embase,

version, including special features used (eg explosion)		CINAHL, Google Scholar
Use of hand searching (eg reference lists of obtained articles)	7	Grey literature and reference lists were hand searched
List of citations located and those excluded, including justification	Figure 1	See Figure 1
Method of addressing articles published in languages other than English	8	There was no limitation on language and articles were translated by health care professionals with an adequate level of understanding.
Method of handling abstracts and unpublished studies	8	Abstracts were included if there was sufficient information to assess the study quality and association between the variable and the outcome
Description of any contact with authors	8	Effort was made to contact authors where appropriate although no replies were received.
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5,6, 8	Detailed inclusion and exclusion criteria are described in main text.
Rationale for the selection and coding of data (eg sound clinical principles or convenience)	8	A data extraction sheet was developed (available on request) and information extraction is described in main text.
Assessment of confounding (eg comparability of cases and controls in studies where appropriate)	12	Different control groups were used, which are outlined in the text.
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8, Figure 2	STROBE was used as described in text.
Assessment of heterogeneity	9	Heterogeneity was explored by assessing the distribution of results in the Forest plots and I-squared.
Description of statistical methods (eg complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	9-11	See text for details
Provision of appropriate tables and graphics	Figures 1-5, Appendix C Supplementary File Table 1	See text for details
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Figures 3-5, Appendix C	Forest plots were provided for all meta-analyses.
Table giving descriptive information for each study included	Supplementary File Table 1	Detailed in Table 1
Results of sensitivity testing (eg subgroup analysis)	14-15 Table 2	Detailed in text and table 2.
Indication of statistical uncertainty of	14-15	Detailed in text. 95% CI reported and I^2

findings		where appropriate.
Reporting of discussion should include		
Quantitative assessment of bias (eg publication bias)	12-13	Detailed in text
Justification for exclusion (eg exclusion of non-English language citations)	5	The exclusion criteria were based on affecting the potential prognostic factors
Assessment of quality of included studies	12-13 Figure 2	STROBE was used, the results are detailed in text and Figure 2
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	16-19	Detailed in text
Generalization of the conclusions (eg appropriate for the data presented and within the domain of the literature review)	16-19	Detailed in text
Guidelines for future research	19-20	Detailed in text
Disclosure of funding source	1	FLM is funded by the Richard and Jack Wiseman Trust (Registered charity number: 1036690).

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson, D, Rennie D, Moher D, Becker, BJ, Sipe TA, Thacker SB for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. **Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting** JAMA. 2000;283(15):2008-2012.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-11

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7, 8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary File Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-13 Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-15 Appendix B Appendix C
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-15 Appendix B Appendix C
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 3b, 4b, 5b
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-15 Appendix B Appendix C
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17

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Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19-20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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