Accepted for publication in Journal of Psychosomatic Obstetrics and Gynecology

A systematic review and meta-analysis of lifestyle predictors of successful assisted reproductive technologies

S, Purewal[1,4]., S.C. E. Chapman[2]., & O.B.A van den Akker[3,] .

[1,4]. Corresponding author: Institute of Psychology, Faculty of Education, Health and Wellbeing, University of Wolverhampton, Wolverhampton, WV1 1AD, UK. Satvinder.purewal@wlv.ac.uk

[2.] Department of Pharmacy & Pharmacology, University of Bath, Claverton Down Road, Bath, BA2 7AY UK

[3.] Corresponding author: Department of Psychology, School of Science and Technology, Middlesex University, London, NW4 4BT, UK

A systematic review and meta-analysis of lifestyle and body mass index predictors of successful assisted reproductive technologies

Abstract

Lifestyle (smoking, drinking alcohol) and body mass index (BMI) predictors of successful outcomes in assisted reproductive technology (ART) treatments were examined in this meta-analysis. **Method:** A bibliographic search was undertaken using 6 databases. The review was informed by PRISMA/MOOSE guidelines. Meta-analytic data were analysed using random effects models. **Results**: We included 77 studies examining effects of BMI, smoking and drinking alcohol. Patients with a BMI <=24.9 were significantly more likely to achieve LB/pregnancy than with BMI >=25 OR=1.219 (95% CI:1.128-1.319, z=4.971, p<001; I^2=53.779%, p=0.001). Non-smokers were significantly more likely to achieve a LB or pregnancy than smokers OR=1.457 (95% CI:1.228-1.727, z=4.324, p< 0.001; I^2=51.883; p=0.001). Meta-regression revealed the number of embryos transferred significantly moderated the effects of smoking on ART outcomes, and there was a trend indicating primary infertility and high BMI were also significant moderators. The evidence for drinking alcohol was inconclusive due to the small number of studies. **Conclusion**: This meta-analysis confirms that ART treatment success can be predicted with lifestyle factors. Further, non-smokers' relative odds of pregnancy/live birth increase as more embryos were transferred but there was a trend that the odds of pregnancy/live birth decrease with primary infertility and high BMI.

Introduction

It is estimated that one in six couples will experience infertility, which is defined as a failure to achieve pregnancy after regular sex for 1 year, and increasingly couples are seeking assisted reproductive technology (ART) [1]. Success rates of a single cycle of ART vary worldwide, with US and UK clinics reporting some of the highest rates between 2012–2013 (29% and 26% respectively), and Japan reporting the lowest (5%) [2]. Women who undertake ART often report 'unhealthy lifestyles'. For example, Domar et al [3] . found that during their IVF treatment, just under 50% of women drank alcohol and 2% reported smoking. Whereas, another recent study [4] also found high rates of alcohol consumption (50.8%) and less than half of women who consumed alcohol regularly reduced their intake and 60% did not reduce consumption of caffeinated drinks. Further, the majority did not change their BMI (83.6%) ahead of fertility treatment.

Research on the effect of lifestyle variables such as obesity, smoking and alcohol consumption on assisted reproductive technologies (ART) outcomes has often been inconsistent. Narrative reviews have reported a negative impact of maternal obesity on ART outcomes [5-6] and positive effects of weight loss on improving ART pregnancy rates [7], and these have been supported by systematic reviews/meta-analytic evidence [8]. Other meta-analytic reviews [9] reported small effects for BMI on ART outcome, or insufficient evidence to support the link between high BMI and lower birth rates, [10], and no associations between obesity and chance of pregnancy after IVF using donor oocytes [11].

Unlike obesity, smoking has much more consistently been found to be detrimental to reproductive health and fertility outcomes [12]. However, the evidence synthesis on the effects of smoking is out-dated [13-15] with some recent empirical evidence demonstrating no effects of maternal and paternal smoking on IVF outcomes [16]. The effects of alcohol on fertility and fertility treatment is inconclusive [17-18], although a review of 2 studies demonstrated decreased pregnancy rates for couples who drank alcohol before or during their treatment [19].

It is possible that one of the reasons for these inconsistencies reported in systematic reviews and meta-analysis on lifestyle data is due to the fact that most previous research, has only examined if BMI and lifestyle factors (including smoking and alcohol consumption) directly predict ART outcomes, without sufficient investigation into whether they also act as moderators for each other on ART outcomes. This is important because these BMI and lifestyles behaviours are often comorbid, although the relationship is complex. For example, a study of 499,504 adults (31 to 69 years) [20] found current smokers were less likely to be obese than never smokers but former smokers were more likely to be obese than current smokers. Further, the risk of obesity increased with the number of cigarettes smoked and decreased from quitting. However, there is a clear association between increased amount of alcohol drank and increased risk of obesity [21].

The objectives of this meta-analysis were therefore to reconcile previous research and examine: a) whether lifestyle factors predict ART treatment success for female patients; and b) whether lifestyle and BMI factors moderate each other.

Methods

Search strategy

This systematic review and meta-analysis was organised and structured according to PRISMA and MOOSE guidelines [22]. A bibliographic search evaluating lifestyle predictors of IVF outcomes (pregnancy or live birth) was undertaken using PubMed, PsycInfo, Embase, ScienceDirect, Web of Science and Scopus. The search was last updated in November 2016. In PubMed, the search terms in titles and abstracts were: (“IVF” OR “intracytoplasmic” OR “intracytoplasmic sperm injection” OR “in vitro fertilization” OR “ICSI” OR “assisted reproductive technology” OR “in vitro fertilisation”) AND (“BMI” OR “body mass index” OR “smoke” OR “smoking” OR “alcohol” OR “drinking”) AND (“pregnancy” OR “live birth” OR “birth rates” or “pregnant”). The search was limited to English language journal articles published after 1978/01/01, concerning humans only. Similar search engine appropriate terms were used in the remaining databases. References cited in previous review papers were also hand searched [e.g., 10-11, 13-14].

,

Study selection

Studies were included if they were published as peer reviewed journal articles; available in English; presented original data; ART treatment included IVF, ICSI, ZIFT, GIFT, treatments such as IUI were excluded because they are not ART. Prospective and retrospective designs were eligible. If it was not possible to calculate unadjusted effect sizes for predictor variables studies were excluded, as were studies of surrogates and oocyte donors/recipients. Where studies reported overlapping data, the study with the largest number of participants was included in the meta-analysis. Data from large national or worldwide databases were excluded

because they often included oocyte donation data, often did not specify which ART techniques were used and posed a risk of multiple report publications.

BMI studies were included if they investigated a link between women's BMI and treatment outcome. It was expected that there would be some variation between studies on their classification of BMI groupings, although standard WHO classifications of BMI groups are normal weight 19-24.9 BMI; overweight 25-29.9 BMI; and obese >30 BMI (WHO, 2006). Based upon WHO classifications, three BMI groups were compared: <=24.9 vs >=25 BMI; 19-24.9 BMI vs 25-29.9 BMI; and 25-29.9 vs 30-34.9 BMI. Studies which did not match WHO criteria were included if it was possible to combine results into the criteria adapted to allow meaningful data analyses. For example, boundaries approximating WHO categories within 1 unit of BMI were combined within the same analyses. No significant differences in effect sizes were found between WHO cut-off levels (i.e., <=24.9 vs >=25 BMI) and studies using cut-offs within 1 unit of BMI criteria (e.g., <=24 vs >24 BMI) ($Q=0.175$, df, 1, $p=0.676$)

Smoking studies were included if they tested for an association between female smoking at the time of treatment and ART outcomes. Alcohol studies were selected if they tested for an association between female patients' alcohol consumption and ART outcome. For both lifestyles, continuous and categorical data were included.

Data screening and extraction

The first author independently screened titles, abstracts and full-text reports of all search results and these were cross-checked by the second author, following

PRISMA guidelines [23]. Disagreements were resolved by discussion. The selection of studies was informed by the research question, inclusion/exclusion criteria, and full consensus by all authors. Data extracted included all independent (BMI; smoking and alcohol consumption) and dependent variables (live birth or pregnancy) and sample sizes. When two or more dependent variables were reported (e.g., serum pregnancy, clinical pregnancy and live birth), the data which is considered 'gold standard' was recorded (in this case, live birth) [24]. Additional data was also inputted, including patient characteristics (female age, average sample BMI, percentage of smokers in sample, number of oocytes retrieved, duration of infertility, previous unsuccessful ART, percentage primary infertility, percentage tubal infertility); treatment characteristics (country, ICSI (all/some vs no ICSI), number of embryos transferred, single or multiple cycle, pregnancy verification (pregnancy test vs ultrasound scan), and study characteristics (date; design (prospective or retrospective).

Risk of bias: study quality

Newcastle-Ottawa Scale (NOS) [25] was used to assess the quality of cohort studies in the meta-analysis. Each paper was independently assessed by SP and OvdA and cross checked with each other to reach 100% consensus through discussion. The scale awarded a maximum of nine stars to each study: four stars for the adequate selection of participants, two stars for comparability of pregnancy/live birth and no pregnancy/live birth groups, and three stars for the adequate ascertainment of the exposure in groups. We defined studies of high quality as those that scored seven-nine stars on the Newcastle-Ottawa scale; studies of medium quality scored five-six stars and studies of low quality of scoring four or less stars.

Data analyses

Data were analysed using Comprehensive Meta-Analysis [26]. For BMI and lifestyle analysis, data were converted to odds ratios for pregnancy or live birth. For all studies, a weighted effect size was calculated using random effects models.

Sensitivity analyses were conducted to examine whether effects were robust under different methodological assumptions: 1) live birth and pregnancy data are included; 2) pregnancy ultrasound scan results and pregnancy test results are used; 3) results were from a single cycle; 4) IVF, ICSI or combined IVF/ICSI treatments are used: 5) prospective designs; 6) high quality studies were included; and 7) Studies were recent (published within the last 7 years -2010- was considered as recent).

We quantified heterogeneity in study effect sizes using the I^2 statistic. If significant heterogeneity was found and more than 10 studies (as previously recommended [27]) provided data on putative moderating variables, the impact of seven factors which have been found to be associated with fertility treatment outcomes was tested [28]. Moderator analyses using 1) meta-regression for average age of the women sampled, average BMI of sample, percentage of smokers in sample, embryos transferred, and oocytes retrieved, and percentage of patients with primary infertility, tubal infertility and average duration of infertility (years) and 2) between group analysis comparing first time ART users vs previous unsuccessful users.

We tested for the presence of publication bias by examining funnel plots for evidence of asymmetry, using Duval and Tweedie's trim and fill method to impute studies where evidence of asymmetry was present. We tested for the significance of these effects using Egger's t-test.

Results

Search Results

See PRISMA flow chart (Fig 1) for searches resulting in 77 included studies.

Study characteristics

Of the 77 studies included; 47 investigated BMI (table 1), 28 smoking (table 2), and two alcohol consumption (table 3), totalling data from 60370 patients (and 7585 cycles). Sample sizes were modest to large, retrospective (n=50) and involved IVF treatment only (n=27) or with ICSI (n=47).

Study quality: Most BMI studies were rated as high quality (n=10) or medium (n=36). Publication date varied considerably; with 27 studies published during and after 2010. Most studies met cut off values for BMI WHO classifications (n=35). Live birth outcome data was reported for 20 studies.

Most smoking studies were rated high quality (n=7) or medium quality (n=17) and were published before 2010 (n=18). Smoking status was typically self-reported and based on number of cigarettes smoked each day. However, four studies used physiological tests to detect smoking (cotinine or Rhodanide concentrations). Live birth outcome data was reported for 10 studies (see table 2).

For alcohol studies, Table 3 shows that Matalliotakis et al [88] was rated as high quality and published before 2010, did not record units of alcohol drunk and reported pregnancy data. Whereas, Rossi et al. [101] was rated as medium quality and

published after 2010. Alcohol drinkers were defined as patients who drank >50g of alcohol per week and used live birth outcomes.

BMI

Main analysis for BMI <=24.9 and patients whose BMI was >=25: Forty seven studies allowed for a comparison between patients with a BMI <=24.9 and >=25 [29-75]. Patients with a BMI <=24.9 were significantly more likely to achieve LB or pregnancy than with a BMI >=25 OR=1.219 (95% CI:1.128-1.319, z=4.971, p<001). Heterogeneity was significant (I^2=53.779%, p=0.001). See figure 2 for forest plot. There was no moderating role of age, the number of embryos transferred, number of oocytes retrieved, duration of infertility and tubal infertility, ART naïve vs previous ART use. There was insufficient data for smoking and primary infertility.

Sensitivity analysis: The effect of BMI with pregnancy or live birth data, single cycle, combination of IVF and ICSI, prospective design, BMI data collected before start of treatment, high quality and recent studies was significant and robust under different methodological assumptions. See Table 4 for further details.

Analysis of normal weight versus overweight patients: Additional analysis using 22 studies of normal weight patients (19-24.9 BMI) and overweight patients (25-29.9 BMI) were compared [29-30, 32, 34-35, 41, 43, 45, 48, 49, 54, 55-57, 60, 62-64, 70-72, 74]. Normal weight patients were significantly more likely to achieve a LB or pregnancy than overweight patients OR=1.168 (95% CI:1.061-1.286, z=3.159, p<002). There was significant heterogeneity (I^2<48.589%, p=0.006). The forest plot of these additional BMI data and sensitivity is not presented but available upon request.

Analysis of overweight versus obese patients: Overweight patients (25-29.9 BMI) were also compared to obese patients (30-34.9 BMI) in nine studies [41, 48, 55, 60, 63, 70-2, 74]. Overweight patients were not significantly different in treatment outcome than obese patients OR=1.219 (95% CI:0.965-1.540; z=1.662: p=.097). There was significant heterogeneity (I^2=60.848; p=0.009).

Smoking

Main analysis: Pregnancy and live birth outcomes Twenty eight studies were included in the meta-analyses [39, 76-100]. Non-smokers were significantly more likely to achieve a LB or pregnancy than smokers OR=1.457 (95% CI:1.228-1.727, z=4.324, p<0.001). Heterogeneity was moderate (I^2=51.883; p=0.001). See figure 3 for a forest plot for the positive effect of not smoking on outcomes. There was a significant moderating effect of number of embryos transferred; non-smokers' relative odds of pregnancy or live birth increased as more embryos were transferred ln(OR) = -0.791 + 0.527(number of embryos transferred) F(1,10) = 9.39, p = 0.01. Although the number of studies were less than 10, analysis revealed a trend that the benefits of non-smoking decreases with higher BMI ln(OR)=2.279+ -0.086, Q(1,8 =9.637, p=0.001). Similarly there was a trend using studies with a higher number of women experiencing primary infertility, that the benefits of not smoking were less evident ln(OR)=2.404 -2.928(% of women with primary infertility), F(1,7) =6.57, p = 0.037. Effect sizes were not significantly moderated by average female age, number of oocytes retrieved, first or multiple ART users, tubal cause and duration of infertility.

Sensitivity analysis: The evidence for smoking was consistent under different methodological conditions (see table 4).

Alcohol

Main analysis: Pregnancy and live birth outcomes: Two studies were available for the alcohol analyses [88, 101]. There was no significant effect of alcohol consumption on ART outcome OR=1.072 (95% CI: 0.630-1.822, z=0.256, p=0.798). Heterogeneity within this analysis was moderate but non-significant (I^2=61.673%, p=0.106). There were too few studies to investigate moderator effects or conduct sensitivity analyses.

Publication bias analyses

There was evidence of publication bias in BMI data for <=24.9 vs>=25 and smoking data. Regarding BMI, trim and fill analyses suggested 8 studies were needed for the funnel plot to be symmetrical and Egger's meta regression intercept was significant (t(45) = 0.863, 95% CI:0.0231.703 p=0.04). This was also true for the smoking analysis. Trim and fill analysis revealed 6 studies were needed for a symmetrical funnel plot. However, Egger's meta-regression intercept was not significant (t(7) = 0.674, 95% CI:-0.201-1.549 p=0.125). Publication bias analysis was not conducted on the alcohol use studies due to the small number of papers available.

Discussion

The aims of these meta-analyses were to examine whether lifestyle factors predict ART treatment success for female patients and whether life style and BMI factors moderate each other. This large, comprehensive meta-analysis found consistent evidence that being overweight/obese and smoking decreases the odds of achieving positive ART outcomes, confirming some meta-analyses [8, 13]. The research evidence for alcohol shows this is not a reliable predictor for ART success or failure,

although the number of studies investigating the effect of alcohol consumption and ART outcomes remains limited.

Critical discussion

Heterogeneity for the BMI and smoking data were significant. Sensitivity analyses for BMI revealed no moderating effect of other variables. However, number of embryos transferred moderated smoking and there was a trend (using less than 10 studies) that primary infertility and high BMI significantly moderated the effects of smoking on ART outcomes. So, a patient who did not smoke, will not see any benefits of not smoking on her ART outcomes if she has a BMI over 25. However, this data must be interpreted with caution because of the small number of studies and clearly more research is necessary. However, this trend is consistent with previous research which has demonstrated the associations between smoking and BMI [20].

A serious shortcoming is the lack of research into the effects of alcohol on ART outcomes. Likewise, Nicolau et al., [19] reported a significant effect (OR 0.84), and also only included two studies. The lack of research into alcohol intake and ART outcomes is surprising as the harmful effects of binge or heavy drinking on pregnancy are well known [102] and drinking alcohol is common and increasing in most countries. For example, in the UK it is estimated that 68% of men and 54% of women drink alcohol [103] and The National Institute for Health and Clinical Excellence advises women who are pregnant or trying to conceive to avoid drinking alcohol [102]. More research is urgently needed to investigate the effect alcohol has on ART outcomes, particularly as this information is important for patients and clinicians.

Studies that have measured alcohol and smoking relied heavily on self-disclosure from patients, although a few used independent, physiological tests to help confirm smoking status based on concentrations of cotinine or Rhodanide [e.g., 83, 86]]. Although ART patients are often advised to stop smoking, reliance on self-reported smoking status was underestimated by 25% in a study of pregnant women. [104]. It is therefore possible that the data used to calculate pooled effect sizes underestimate the effects of smoking and possibly alcohol intake on ART outcomes.

Finally, there was some evidence of a tendency for small studies with high variance to be published more often when they showed an effect for BMI or smoking, suggesting that the 'file drawer problem' might bias the published literature on these topics. Our meta-regression analyses were also based upon published averages of patient characteristics such as age or number of oocytes retrieved. It should be noted that these results may be different to (and less reliable) than individual patient data because of the potential for misleading conclusions and aggregation bias [105]. There are also problems with consistency among definition and classification of study variables. For example, many BMI studies did not have cut off values or they were varied and did not follow WHO recommendations for classifications which created difficulties in combining study results and comparing BMI groups. Consequently, some studies were excluded from the quantitative synthesis and the meta-analysis lost some precision because a few studies were combined to make full use of all the available data. However, despite these methodological shortcomings in the extracted data, there was limited statistical heterogeneity, suggesting BMI study results are valid and consistent with previous meta-analyses.

The conclusions of this meta-analysis are that lifestyle factors that include BMI and smoking are contributing factors to poorer ART outcomes. More research is warranted to investigate the moderating role of psychological variables on lifestyle factors including obesity and smoking.

Current knowledge on the subject

- Research evidence for the effect of BMI on ART outcomes are often inconsistent.
- Smoking has consistently been found to be detrimental to fertility outcomes but the effects of alcohol on ART outcomes is inconclusive.
- Further, there is a need to investigate whether life style and BMI factors moderate each other on ART outcomes.

What this study adds

- This large, comprehensive meta-analysis of published studies found consistent evidence that being overweight/obese and smoking significantly decreases the odds of achieving positive ART outcomes.
- The effects of alcohol on ART outcomes were not significant.
- Smoking is moderated by number of embryos transferred and there was some data to suggest primary infertility and high BMI was moderated by smoking.

Acknowledgements

The authors would like to acknowledge the help of Subarna Roy for retrieving articles.

Funding

This research was funded by the British Academy small grant award (SG100026).

Declaration of interests

The authors have no interests to declare.

References

1. Farquhar, C., et al ., *Assisted reproductive technology: an overview of Cochrane Reviews.* The Cochrane Library.
2. Kushnir, V. A. et al, *Systematic review of worldwide trends in assisted reproductive technology 2004–2013.* Reprod. Biol. Endocrinol, 2017. **15**(1): p. 6.
3. Domar, A., et al, *Lifestyle behaviors in women undergoing in vitro fertilization: a prospective study,* Fertil Steril, 2012. **97**(3): p. 697-701.
4. Gormack, A. A., et al, *Many women undergoing fertility treatment make poor lifestyle choices that may affect treatment outcome*. Hum Reprod, 2015. **30** (7): p. 1617-1624.
5. Brewer, C.J. and A.H. Balen, *The adverse effects of obesity on conception and implantation.* Reproduction, 2010. **140**(3): p. 347-364.
6. Kumbak, B., E. Oral, and O. Bukulmez, *Female obesity and assisted reproductive technologies.* Semin Reprod Med, 2012. **30**(6): p. 507-16.
7. Talmor, A. and B. Dunphy, *Female obesity and infertility.* Best Practice & Research Clinical Obstetrics & Gynaecology, 2015. **29**(4): p. 498-506.
8. Rittenberg, V., et al., *Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis.* Reprod Biomed Online, 2011. **23**(4): p. 421-39.
9. Koning, A.M., et al., *Complications and outcome of assisted reproduction technologies in overweight and obese women.* Hum Reprod, 2012. **27**(2): p. 457-67.
10. Maheshwari, A., L. Stofberg, and S. Bhattacharya, *Effect of overweight and obesity on assisted reproductive technology--a systematic review.* Hum Reprod Update, 2007. **13**(5): p. 433-44.
11. Jungheim, E.S., et al., *IVF outcomes in obese donor oocyte recipients: a systematic review and meta-analysis.* Hum Reprod, 2013. **28**(10): p. 2720-7.
12. Dechanet, C., et al., *Effects of cigarette smoking on reproduction.* Human reproduction update, 2011. **17**(1): p. 76-95.
13. Waylen, A., et al., *Effects of cigarette smoking upon clinical outcomes of assisted reproduction: a meta-analysis.* Human reproduction update, 2009. **15**(1): p. 31-44.
14. Augood, C., K. Duckitt, and A. Templeton, *Smoking and female infertility: a systematic review and meta-analysis.* Human Reproduction, 1998. **13**(6): p. 1532-1539.
15. Feichtinger, W., et al., *Smoking and in vitro fertilization: a meta-analysis.* Journal of assisted reproduction and genetics, 1997. **14**(10): p. 596-599.
16. Cinar, O., et al., *Does cigarette smoking really have detrimental effects on outcomes of IVF?* European Journal of Obstetrics & Gynecology and Reproductive Biology, 2014. **174**: p. 106-110.
17. Agarwal, A., et al., *The effects of oxidative stress on female reproduction: a review.* Reproductive Biology and Endocrinology, 2012. **10**(1): p. 49.
18. Homan, G.F., M. Davies, and R. Norman, *The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review.* Hum Reprod Update, 2007. **13**(3): p. 209-23.
19. Nicolau, P., et al., *Alcohol consumption and in vitro fertilization: a review of the literature.* Gynecol Endocrinol, 2014. **30**(11): p. 759-63.
20. Dare, S., Mackay, D.F., and J.P. Pell, *Correction: Relationship between Smoking and Obesity: A Cross-Sectional Study of 499,504 Middle-Aged Adults in the UK General Population.* PLOS ONE, 2017. **12**(2): e0172076.
21. Traversy, G., and J.P. Chaput, (2015). *Alcohol consumption and obesity: an update*. Curr Obes Rep, 2015. **4**(1): p. 122-130.
22. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting.* Jama, 2000. **283**(15): p. 2008-2012.
23. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* J Clin Epidemiol, 2009. **62**(10): p. 1006-12.

24. Maheshwari, A., S. Bhattacharya, and N.P. Johnson, *Predicting fertility.* Hum Fertil (Camb), 2008. **11**(2): p. 109-17.
25. Wells, G. A., et al, *The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses.* 2009. Epub Available from: URL: http://www. ohri. ca/programs/clinical_epidemiology/oxford. htm [cited 2009 Oct 19].
26. Borenstein, M., et al., *Comprehensive meta-analysis version 2.* Englewood, NJ: Biostat, 2005. **104**.
27. Deeks, J., P. Bossuyt, and C. Gatsonis, *Cochrane handbook for systematic reviews of diagnostic test accuracy version 1.0. 0.* The Cochrane Collaboration, 2009.
28. Templeton, A., J.K. Morris, and W. Parslow, *Factors that affect outcome of in-vitro fertilisation treatment.* The Lancet, 1996. **348**(9039): p. 1402-1406.
29. Bellver, J., et al., *Female obesity impairs in vitro fertilization outcome without affecting embryo quality.* Fertility and sterility, 2010. **93**(2): p. 447-454.
30. Dechaud, H., et al., *Obesity does not adversely affect results in patients who are undergoing in vitro fertilization and embryo transfer.* European Journal of Obstetrics & Gynecology and Reproductive Biology, 2006. **127**(1): p. 88-93.
31. Dokras, A., et al., *Obstetric outcomes after in vitro fertilization in obese and morbidly obese women.* Obstetrics & Gynecology, 2006. **108**(1): p. 61-69.
32. Esinler, I., G. Bozdag, and H. Yarali, *Impact of isolated obesity on ICSI outcome.* Reproductive biomedicine online, 2008. **17**(4): p. 583-587.
33. Farhi, J., et al., *High-quality embryos retain their implantation capability in overweight women.* Reproductive biomedicine online, 2010. **21**(5): p. 706-711.
34. Fedorcsák, P., et al., *Impact of overweight and underweight on assisted reproduction treatment.* Human Reproduction, 2004. **19**(11): p. 2523-2528.
35. Kilic, S., et al., *Obesity alters retrieved oocyte count and clinical pregnancy rates in high and poor responder women after in vitro fertilization.* Arch Gynecol Obstet, 2010. **282**(1): p. 89-96.
36. Ku, S.Y., et al., *Clinical efficacy of body mass index as predictor of in vitro fertilization and embryo transfer outcomes.* J Korean Med Sci, 2006. **21**(2): p. 300-3.
37. Lashen, H., et al., *Extremes of body mass do not adversely affect the outcome of superovulation and in-vitro fertilization.* Hum Reprod, 1999. **14**(3): p. 712-5.
38. Li, Y., D. Yang, and Q. Zhang, *Impact of overweight and underweight on IVF treatment in Chinese women.* Gynecol Endocrinol, 2010. **26**(6): p. 416-22.
39. Lintsen, A.M., et al., *Effects of subfertility cause, smoking and body weight on the success rate of IVF.* Human reproduction, 2005. **20**(7): p. 1867-75.
40. Loveland, J.B., et al., *Increased body mass index has a deleterious effect on in vitro fertilization outcome.* J Assist Reprod Genet, 2001. **18**(7): p. 382-6.
41. Maheshwari, A., et al., *The direct health services costs of providing assisted reproduction services in overweight or obese women: a retrospective cross-sectional analysis.* Hum Reprod, 2009. **24**(3): p. 633-9.
42. Marci, R., et al., *Ovarian stimulation in women with high and normal body mass index: GnRH agonist versus GnRH antagonist.* Gynecol Endocrinol, 2012. **28**(10): p. 792-5.
43. Martinuzzi, K., et al., *Elevated body mass index (BMI) does not adversely affect in vitro fertilization outcome in young women.* J Assist Reprod Genet, 2008. **25**(5): p. 169-75.
44. Matalliotakis, I., et al., *Impact of body mass index on IVF and ICSI outcome: a retrospective study.* Reprod Biomed Online, 2008. **16**(6): p. 778-83.
45. Metwally, M., T.C. Li, and W.L. Ledger, *The impact of obesity on female reproductive function.* Obes Rev, 2007. **8**(6): p. 515-23.
46. Moini, A., et al., *The effect of body mass index on the outcome of IVF/ICSI cycles in non-polycystic ovary syndrome women.* Int J Fertil Steril, 2008. **2**(2): p. 82-85.

47. Orvieto, R., et al., *Ovarian stimulation in polycystic ovary syndrome patients: the role of body mass index.* Reprod Biomed Online, 2009. **18**(3): p. 333-6.
48. Özgün, M.T., et al., *The influence of body mass index on FSH dose and pregnancy rate in women undergoing ICSI-embryo transfer.* Journal of the Turkish German Gynecological Association, 2009. **10**: p. 1-5.
49. Pinborg, A., et al., *Influence of female bodyweight on IVF outcome: a longitudinal multicentre cohort study of 487 infertile couples.* Reprod Biomed Online, 2011. **23**(4): p. 490-9.
50. Rabinson, J., et al., *GnRH agonist versus GnRH antagonist in ovarian stimulation: the influence of body mass index on in vitro fertilization outcome.* Fertil Steril, 2008. **89**(2): p. 472-4.
51. Ramezanzadeh, F., et al., *Impact of body mass index versus physical activity and calorie intake on assisted reproduction outcomes.* Eur J Obstet Gynecol Reprod Biol, 2012. **163**(1): p. 52-6.
52. Salha, O., T. Dada, and V. Sharma, *Influence of body mass index and self-administration of hCG on the outcome of IVF cycles: a prospective cohort study.* Hum Fertil (Camb), 2001. **4**(1): p. 37-42.
53. Sathya, A., et al., *Effect of body mass index on in vitro fertilization outcomes in women.* J Hum Reprod Sci, 2010. **3**(3): p. 135-8.
54. Setti, A.S., et al., *Body mass index is negatively correlated with the response to controlled ovarian stimulation but does not influence oocyte morphology in ICSI cycles.* Eur J Obstet Gynecol Reprod Biol, 2012. **163**(2): p. 175-9.
55. Shalom-Paz, E., et al., *Effects of different body mass indices on in vitro maturation in women with polycystic ovaries.* Fertil Steril, 2011. **96**(2): p. 336-9.
56. Singh, N., et al., *Correlation of body mass index with outcome of in vitro fertilization in a developing country.* Arch Gynecol Obstet, 2012. **285**(1): p. 259-63.
57. Sneed, M.L., et al., *Body mass index: impact on IVF success appears age-related.* Hum Reprod, 2008. **23**(8): p. 1835-9.
58. van Swieten, E.C., et al., *Obesity and clomiphene challenge test as predictors of outcome of in vitro fertilization and intracytoplasmic sperm injection.* Gynecologic and obstetric investigation, 2005. **59**(4): p. 220-224.
59. Vilarino, F.L., et al., *Body mass index and fertility: is there a correlation with human reproduction outcomes?* Gynecological Endocrinology, 2011. **27**(4): p. 232-236.
60. Wang, J., M. Davies, and R. Norman, *Body mass and probability of pregnancy during assisted reproduction treatment: Retrospective study.* British Medical Journal, 2000. **321**(7272): p. 1320.
61. Wittemer, C., et al., *Does body mass index of infertile women have an impact on IVF procedure and outcome?* Journal of assisted reproduction and genetics, 2000. **17**(10): p. 547-552.
62. Zhang, D., et al., *Overweight and obesity negatively affect the outcomes of ovarian stimulation and in vitro fertilisation: a cohort study of 2628 Chinese women.* Gynecological Endocrinology, 2010. **26**(5): p. 325-332.
63. Zander-Fox, D.L., et al., *Does obesity really matter? The impact of BMI on embryo quality and pregnancy outcomes after IVF in women aged≤ 38 years.* Australian and New Zealand Journal of Obstetrics and Gynaecology, 2012. **52**(3): p. 270-276.
64. Akpınar, F., et al, (2014). *Obesity is not associated with the poor pregnancy outcome following intracytoplasmic sperm injection in women with polycystic ovary syndrom*e. J Turk Ger Gynecol Assoc, 2014. **15**(3): p. 144.
65. Bu, Z.,et al., *Overweight and obesity adversely affect outcomes of assisted reproductive technologies in polycystic ovary syndrome patie*nts. International journal of clinical and experimental medicine, 2013. **6**(10): p. 991.

66. Caillon, H., et al, *Effects of female increased body mass index on in vitro fertilization cycles outcome*. Obesity research & clinical practice, 2015. ***9***(4): p. 382-388.
67. Hill, M. J., Hong, S., and J. L., Frattarelli, *Body mass index impacts in vitro fertilization stimulation*. ISRN Obstet Gynecol. *2011*.
68. Huang, K., et al, *Effect of overweight/obesity on IVF-ET outcomes in chinese patients with polycystic ovary syndrome*. Int J Clin Exp Med, 2014. ***7***(12): p. 5872.
69. Inal, H. A., et al*, The impact of follicular fluid adiponectin and ghrelin levels based on BMI on IVF outcomes in PCOS*. J Endocrinol Invest, 2014. **39**(4): p. 431-437.
70. Kalem, M. N., et al, *Effect of body mass index and age on in vitro fertilization in polycystic ovary syndrome*. J Turk Ger Gynecol Assoc, 2016. **17**(2): p. 83.
71. Ozekinci, M., et al, *Does obesity have detrimental effects on IVF treatment outcomes?.* BMC women's health, 2015. **15**(1): p. 61.
72. Petanovski, Z., G., et al*, Impact of body mass index (BMI) and age on the outcome of the IVF process*. Prilozi, 2011. *32*(1): p. 55-71.
73. Rittenberg, V., et al, *Influence of BMI on risk of miscarriage after single blastocyst transfer*. Hum Reprod 2011. **26** (10): p. 2642-2650.
74. Schliep, K.C., et al, *Effect of male and female body mass index on pregnancy and live birth success after in vitro fertilization*. Fertil Steril, 2015. **103**(2): p. 388-395.
75. Vural, F., Vural, B., and Y. Çakiroglu, *In vitro fertilization outcomes in obese women under and above 35 years of age*. Clin Exp Obstet Gynecol, 2016. **43**(2): p. 233-7
76. Al-Saleh, I., et al., *The effect of caffeine consumption on the success rate of pregnancy as well various performance parameters of in-vitro fertilization treatment.* Medical Science Monitor Basic Research, 2010. **16**(12): p. CR598-CR605.
77. Ben-Haroush, A., et al., *High-quality embryos maintain high pregnancy rates in passive smokers but not in active smokers.* Reproductive biomedicine online, 2011. **22**(1): p. 44-49.
78. Chung, P., et al., *Gamete intrafallopian transfer. Does smoking play a role?* The Journal of reproductive medicine, 1997. **42**(2): p. 65-70.
79. Crha, I., et al., *The outcome of infertility treatment by in-vitro fertilisation in smoking and non-smoking women.* Central European journal of public health, 2001. **9**(2): p. 64-68.
80. Dessolle, L., et al., *Predictive factors of healthy term birth after single blastocyst transfer.* Human reproduction, 2011. **26**(5): p. 1220-1226.
81. El-Nemr, A., et al., *Effect of smoking on ovarian reserve and ovarian stimulation in in-vitro fertilization and embryo transfer.* Human Reproduction, 1998. **13**(8): p. 2192-2198.
82. Freour, T., et al., *Ovarian reserve and in vitro fertilization cycles outcome according to women smoking status and stimulation regimen.* Archives of gynecology and obstetrics, 2012. **285**(4): p. 1177-1182.
83. Fuentes, A., et al., *Recent cigarette smoking and assisted reproductive technologies outcome.* Fertility and sterility, 2010. **93**(1): p. 89-95.
84. Gruber, I., et al., *Effect of a woman's smoking status on oocyte, zygote, and day 3 pre-embryo quality in in vitro fertilization and embryo transfer program.* Fertility and sterility, 2008. **90**(4): p. 1249-1252.
85. Hannoun, A., et al., *Effect of female nargile smoking on in vitro fertilization outcome.* Eur J Obstet Gynecol Reprod Biol, 2010. **150**(2): p. 171-4.
86. Hughes, E.G., et al., *Cigarette smoking and the outcomes of in vitro fertilization: measurement of effect size and levels of action.* Fertil Steril, 1994. **62**(4): p. 807-14.
87. Joesbury, K.A., et al., *Evidence that male smoking affects the likelihood of a pregnancy following IVF treatment: application of the modified cumulative embryo score.* Hum Reprod, 1998. **13**(6): p. 1506-13.
88. Matalliotakis, I., et al., *Epidemiological factors influencing IVF outcome: Evidence from the Yale IVF program.* J Obstet Gynaecol, 2008. **28**(2): p. 204-8.

89. Maximovich, A. and S.A. Beyler, *Cigarette smoking at time of in vitro fertilization cycle initiation has negative effect on in vitro fertilization-embryo transfer success rate.* J Assist Reprod Genet, 1995. **12**(2): p. 75-7.
90. Pattinson, H.A., P.J. Taylor, and M.H. Pattinson, *The effect of cigarette smoking on ovarian function and early pregnancy outcome of in vitro fertilization treatment.* Fertil Steril, 1991. **55**(4): p. 780-3.
91. Petanovski, Z., et al., *Impact of active female smoking on controlled ovarian stimulation in intracytoplasmic sperm insemination cycles.* Med Glas (Zenica), 2012. **9**(2): p. 273-80.
92. Sharara, F.I., et al., *Cigarette smoking accelerates the development of diminished ovarian reserve as evidenced by the clomiphene citrate challenge test.* Fertil Steril, 1994. **62**(2): p. 257-62.
93. Sterzik, K., et al., *Influence of smoking on fertility in women attending an in vitro fertilization program.* Fertility and sterility, 1996. **65**(4): p. 810-814.
94. Tiboni, G., et al., *Influence of cigarette smoking on vitamin E, vitamin A, β-carotene and lycopene concentrations in human pre-ovulatory follicular fluid.* International journal of immunopathology and pharmacology, 2004. **17**(3): p. 389-393.
95. Trapp, M., P. Kemeter, and W. Feichtinger, *Smoking and in-vitro fertilization.* Human Reproduction, 1986. **1**(6): p. 357-358.
96. Weigert, M., et al., *The effect of smoking on oocyte quality and hormonal parameters of patients undergoing in vitro fertilization–embryo transfer.* Journal of assisted reproduction and genetics, 1999. **16**(6): p. 287-293.
97. Van Voorhis, B.J., et al., *The effects of smoking on ovarian function and fertility during assisted reproduction cycles.* Obstetrics & Gynecology, 1996. **88**(5): p. 785-791.
98. Wright, K., et al., *The effect of female tobacco smoking on IVF outcomes.* Human Reproduction, 2006. **21**(11): p. 2930-2934.
99. Fréour, T,. et al, *Comparison of embryo morphokinetics after in vitro fertilization-intracytoplasmic sperm injection in smoking and nonsmoking women*. Fertil Steril, 2013. **99**(7):p. 1944-1950.
100. Neal, M. S., Zhu, J., and W. G. Foster, *Quantification of benzo [a] pyrene and other PAHs in the serum and follicular fluid of smokers versus non-smokers.* Reprod Toxicol, 2008. **25**(1): p. 100-106.
101. Rossi, B.V., et al., *Effect of alcohol consumption on in vitro fertilization.* Obstet Gynecol, 2011. **117**(1): p. 136-42.
102. National Institute for Health and Care Excellence. "Antenatal care for uncomplicated pregnancies." NICE clinical guidelines. Updated edition. London (2008). CG62.
103. Health and Social Care Information Centres, *Statistics on Alcohol: England, 2012*. 2012.
104. Shipton, D., et al., *Reliability of self reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study.* BMJ, 2009. **339**: p. b4347.
105. Thompson, S.G. and J. Higgins, *How should meta-regression analyses be undertaken and interpreted?* Statistics in medicine, 2002. **21**(11): p. 1559-1573.

Table 1: Study characteristics of body mass index (BMI) studies

Authors	Variable/ classification	Time of assessment	Outcome & assessment of outcome	Design	Sample Size	Treatment	Cycle (single or multiple)	Newcastle-Ottawa Quality Score
1. Akpinar et al 2014	18.5-24.9 BMI 25-29.9 BMI 30-34.5 BMI	Timing not specified	P HCG test	Retrospective	272	ICSI	Multiple	Selection *** Comparability Outcome **
2. Bellver et al 2010	20-24.9 BMI 25-29.9 BMI >=30 BMI	Before stimulation	LB Ultrasound scan	Retrospective	4227	ICSI	Multiple	Selection *** Comparability Outcome ***
3. Bu et al 2013	18.5-24 BMI >=24 BMI	Timing not specified	P Ultrasound scan	Retrospective	688	IVF, ICSI	Single	Selection *** Comparability Outcome ***
4. Caillon et al 2015	18.5-24.9 BMI >=25 BMI	Timing not specified	LB Not specified	Retrospective	558	IVF, ICSI	Single	Selection *** Comparability Outcome ***
5. Dechaud et	<20 BMI >=20-<25 BMI >=25-<30 BMI	Initial consultatio n	P 12 weeks gestation	Retrospective	573	IVF, ICSI	Multiple	Selection *** Comparability

al 2006	>=30 BMI		(pregnancy assessment unspecified)					Outcome ***
6. Dokras et al 2006	<25 BMI 25-29.9 BMI 30-39.9 BMI >=40 BMI	Initial consultation	LB Delivery after 20 weeks gestation	Retrospective	1293	IVF, ICSI	Multiple	Selection *** Comparability Outcome ***
7. Esinler et al 2008	18.5-24.9 BMI 25-29.9 BMI >=30 BMI	Before treatment	P Ultrasound scan	Retrospective	775	ICSI	Multiple	Selection *** Comparability Outcome ***
8. Farhi et al 2010	<=25 BMI >25 BMI	Before treatment	LB (not specified)	Retrospective	233	IVF, ICSI	Single	Selection *** Comparability Outcome ***
9. Fedorcsake t al 2004	<18.5 BMI 18.5-24.9 BMI 25-29.9 BMI >=30 BMI	Initial consultation	LB (not specified)	Retrospective	2660	IVF, ICSI	Multiple	Selection *** Comparability Outcome ***
10. Hill et al 2011	<=25 BMI >25 BMI <30 BMI >=30	Timing not specified	P Ultrasound scan	Prospective	117	IVF	Single	Selection *** Comparability Outcome ***

11. Huang et al 2014	<24 BMI >=24 BMI	Timing not specified	LB Born and survive more than 1 month	Retrospective	256	IVF, ICSI	Single	Selection *** Comparability Outcome ***
12. Inal et al 2016	<25 BMI >=25 BMI	Timing not specified	P Not specified	Prospective	120	IVF	Single	Selection *** Comparability Outcome *
13. Kalem et al 2016	18-24.9 BMI 25-29.9 BMI >=30 BMI	Timing not specified	P Ultrasound scan	Retrospective	653	IVF	Single	Selection *** Comparability Outcome ***
14. Kilic et al 2010	18-24.9 BMI 25-29.9 BMI >=30 BMI	Timing not specified	P Ultrasound scan	Retrospective	1970	IVF	Single	Selection *** Comparability * Outcome ***
15. Ku et al 2006	<24 BMI >=24 BMI	Timing not specified	P Ultrasound scan	Retrospective	223	IVF, ICSI	Multiple	Selection ** Comparability Outcome ***

16. Lashen et al 1999	<19 BMI 20-24 BMI >27.9 BMI	Timing not specified	P (not specified)	Retrospective, case control	333	IVF	Single	Selection *** Comparability Outcome **
17. Li et al 2010	<18.5 BMI >=18.5-23.9 BMI >=24 BMI	Before treatment	LB (not specified)	Retrospective	1107	IVF, ICSI	Single	Selection *** Comparability Outcome ***
18. Lintsen et al 2005	<20 BMI 20-25 BMI 25-27 BMI >=27 BMI	Initial consultation	LB Delivery	Retrospective	8457	IVF	Single	Selection *** Comparability Outcome ***
19. Loveland et al 2001	<=25 BMI >25 BMI	Timing not specified	P Delivered or >20 weeks pregnancy (ultrasound scan)	Retrospective	139	IVF	Multiple	Selection *** Comparability Outcome ***
20. Maheshwari et al 2009	<18.5 BMI 18.5-24.9 BMI 25-29.9 BMI 30-34.5 BMI >=35 BMI	Within 3 months of commencing a cycle	LB Delivery	Retrospective	1756	IVF,ICSI	Single	Selection *** Comparability Outcome ***
21. Marci et al	20-25 BMI >25 BMI	Timing not specified	P Ultrasound scan	Prospective	463	IVF,ICSI	Single	Selection ***

2012								Comparability Outcome ***
22. Martinuzzi et al 2008	<18.5 BMI 18.5-24.9 BMI 25-29.9 BMI >=30 BMI	Initial consultation	P Ultrasound scan	Retrospective	417	IVF,ICSI	Single	Selection *** Comparability Outcome ***
23. Matalliotakis et al 2008a	<=24 BMI >24 BMI	Before treatment	LB Delivery	Retrospective	278	IVF,ICSI	Multiple	Selection *** Comparability Outcome ***
24. Metwally et al 2007b	19-24.9 BMI 25-29.9 BMI >=30 BMI	Timing not specified	P Ultrasound scan	Retrospective	426	IVF, ICSI	Multiple	Selection *** Comparability Outcome ***
25. Moini et al 2008	<20-25 BMI 25-<=30 BMI >30 BMI	Timing not specified	P Ultrasound	Prospective	287	IVF, ICSI	Single	Selection **** Comparability Outcome ***
26. Orvieto et al 2009	<=25 BMI >25 BMI	Timing not specified	P Ultrasound scan	Retrospective	59	IVF	Multiple	Selection *** Comparability **

								Outcome ***
27. Ozekinci et al 2015	18.5-24.9 BMI 25-29.9 BMI >=30 BMI	Timing not specified	P Ultrasound scan	Retrospective	298	IVF, ICSI	Single	Selection *** Comparability Outcome ***
28. Ozgun et al 2009	<18.5 BMI 18.5-24.9 BMI 25-29.9 BMI 30-35.9 BMI >=36 BMI	Before ovulation induction	P Ultrasound scan	Prospective	604	ICSI	Single	Selection **** Comparability Outcome ***
29. Petanovski et al 2011	<18.5 BMI 18.5-24.9 BMI 25-29.9 BMI >=30 BMI	Timing not specified	LB Delivery	Retrospective	920	IVF	Single	Selection *** Comparability Outcome ***
30. Pinborg et al 2011	<18.5 BMI 18.5-24.9 BMI 25-29.9 BMI >=30 BMI	Before treatment	LB Delivery	Prospective	487	IVF,ICSI,FET	Multiple	Selection **** Comparability Outcome ***
31. Rabinson et al 2008	<25 BMI >=25 BMI	Timing not specified	P Not specified	Retrospective	799 cycles	IVF	Multiple	Selection *** Comparability Outcome **

32. Ramezanzadeh et al 2012	<25 BMI >=25 BMI	Day 3 of spontaneous menstrual cycle	P Ultrasound scan	Prospective	236	IVF,ICSI	Unclear	Selection **** Comparability Outcome ***
33. Rittenberg et al 2011	18.5-24.9 BMI >=25 BMI	Within one month of starting treatment	LB Not specified	Prospective	413	IVF, ICSI	Multiple	Selection **** Comparability Outcome ***
34. Salha et al 2001	18-25 BMI >=26 BMI	Timing not specified	P Ultrasound scan	Prospective	100	IVF	Single	Selection *** Comparability * Outcome ***
35. Sathya et al 2010	<25 BMI 25-30 BMI >30 BMI	Timing not specified	P Not specified	Retrospective	308	IVF,ICSI	Unclear	Selection *** Comparability Outcome **
36. Schliep et al 2014	<18.5 BMI 18.5-24.9 BMI 25-29.9 BMI 30-34.9 BMI >=35 BMI	Initial consultation	LB Delivery	Prospective	721	IVF	Single	Selection **** Comparability Outcome ***

37. Setti et al 2012	<19 BMI 19-24.9 BMI 25-29.9 BMI >=30 BMI	Timing not specified	P Not specified	Retrospective	1105	IVF,ICSI	Single	Selection *** Comparability Outcome **
38. Shalom-Paz et al 2011	<20 BMI 20-24 BMI 25-29 BMI 30-34 BMI >=35 BMI	Timing not specified	LB Delivery	Retrospective	113	IVF, ICSI	Multiple	Selection *** Comparability Outcome ***
39. Singh et al 2012	<18.5 BMI 18.5-24.9 BMI 25-29.9 BMI >=30 BMI	Timing not specified	P Not specified	Retrospective	316	IVF,ICSI	Multiple	Selection *** Comparability Outcome **
40. Sneed et al 2008	<18.5 BMI 18.5-24.9 BMI 25-29.9 BMI >=30 BMI	Timing not specified	LB Not specified	Retrospective	1273	IVF	Single	Selection *** Comparability Outcome ***
41. Van Swieten et al 2005	BMI <25 BMI 25-30 BMI >30 BMI	Before down regulation	P HCG test	Prospective	162	IVF, ICSI	Multiple	Selection *** Comparability Outcome **
42. Vilarino et	<25 BMI >=25 BMI	Timing not specified	LB Foetus born	Retrospective	191	IVF, ICSI	Multiple	Selection ***

al 2011			alive beyond 22nd week pregnancy					Comparability Outcome **
43. Vural et al 2016	<25 BMI 25-30 BMI >=30 BMI	Timing not specified	P Ultrasound	Retrospective	780	IVF	Unclear	Selection *** Comparability Outcome ***
44. Wang et al 2000	<20 BMI 20-24.9 BMI 25-29.9 BMI 30-34.9 BMI >=35 BMI	Timing not specified	P Ultrasound	Retrospective	3586	IVF,ICSI,GIFT	Multiple	Selection *** Comparability Outcome ***
45. Wittemer et al 2000	<20 BMI >=20-25 BMI >=25 BMI	Timing not specified	LB Delivery	Retrospective	398	IVF, ICSI	Multiple	Selection *** Comparability Outcome ***
46. Zander-Fox et al 2012	18.5-24.9 BMI 25-29.9 BMI 30-34.9 BMI 35-39.9 BMI >=40 BMI	Before treatment	LB Delivery	Retrospective	2057 cycles	IVF,ICSI	Multiple	Selection *** Comparability Outcome ***
47. Zhang et al 2010	18.5-24.9 BMI 25-29.9 BMI >=30 BMI	30-60 days before cycle	LB Not specified	Retrospective	2628	IVF, ICSI	Single	Selection *** Comparability

								Outcome ***

Note: ART = Assisted reproductive technologies; FET = Frozen embryo transfers; GIFT = Gamete intra-fallopian transfer; ICSI = intracytoplasmic sperm injection; IVT = in vitro fertilisation; LB = live birth outcome data; P= pregnancy outcome data; ZIFT = zygote intrafallopian transfer. The sample size refers to data that is extracted from the papers and used in the meta-analysis.

Table 2: Study characteristics of Smoking studies

Authors	Variable/ classification	Time of assessment	Outcome & assessment of outcome	Design	Sample Size	Treatment	Cycle (single or multiple)	Newcastle-Ottawa Quality Score
1. Al-Saleh et al 2010	Smokers vs Non-smokers (self report)	Timing not specified	P Ultrasound scan	Prospective	619	IVF,ICSI	Single	Selection **** Comparability * Outcome ***
2. Ben-Haroush et al 2011	Smokers vs Non-smokers (self report)	Data collected post-treatment on their smoking status during treatment	LB Not specified	Retrospective	237	IVF,ICSI	Single	Selection ** Comparability Outcome ***
3. Chung et al 1997	Smokers = >1 cigarettes a day Non smokers = 0 cigarettes (self report)	Data collected post-treatment on their smoking status during treatment	LB Not specified	Retrospective	85	GIFT	Single	Selection *** Comparability Outcome ***
4. Crha et al 2001	Smokers = >1 cigarettes a day Non smokers = 0 cigarettes	Before stimulation	P Ultrasound	Prospective	159	IVF	Single	Selection *** Comparability Outcome ***

	(self report)							
5. Dessolle et al 2011	Smokers vs Non-smokers (self report)	Timing not specified	LB Delivery of healthy term singleton	Prospective	872	IVF, ICSI	Single	Selection **** Comparability Outcome ***
6. El-Nemr et al 1998	Smokers >1 cigarettes a day Non-smokers 0 cigarettes a day (self report)	Initial consultation	P Ultrasound scan	Retrospective	173	IVF	Single	Selection *** Comparability Outcome ***
7. Freour et al 2010	Smokers vs Non-smokers (self report)	Initial consultation	P Ultrasound scan	Prospective	384	IVF,ICSI	multiple	Selection **** Comparability * Outcome ***
8. Freour et al 2012	Smokers vs Non-smokers (self report)	Initial consultation	LB Not specified	Prospective	277	IVF	Single	Selection **** Comparability Outcome ***
9. Freour et al 2013	Smokers vs Non-smokers (self report)	Initial consultation	P Ultrasound scan	Retrospective	135	IVF, ICSI	Multiple	Selection *** Comparability Outcome ***

10. Fuentes et al 2010	Smokers vs non-smokers (self-report) and assessment-smokers who had cotinine concentrations and non-smokers who did not)	Before oocyte retrieval	LB (not specified)	Prospective	166	IVF,ICSI	Single	Selection *** Comparability Outcome ***
11. Gruber et al 2008	Smokers vs Non-smokers (self report)	Initial consultation	P Ultrasound scan	Retrospective	130	ICSI	Multiple	Selection *** Comparability Outcome ***
12. Hannoun et al 2010	Smokers vs Non-smokers (self report)	Before oocyte retrieval	P Ultrasound scan	Prospective	246	IVF,GIFT	Single	Selection ** Comparability Outcome **
13. Harrison et al 1990	Smokers >1 cigarettes a day Non-smokers 0 cigarettes a day (self report)	Initial consultation	P Not specified	Prospective	650	IVF, ICSI	Single	Selection **** Comparability Outcome *
14. Hughes et al 1994	Smokers vs non-smokers (self-report and assessment-smokers who had	Self report before and cotinine testing during	P Ultrasound scan	Prospective	316	IVF	Multiple	Selection **** Comparability Outcome ***

	cotinine concentrations and non-smokers who did not)	treatment						
15. Joesbury et al 1998	Smokers vs Non-smokers (self report)	Initial consultation	LB Alive one month post delivery	Retrospective	385	IVF,ICSI	Multiple	Selection *** Comparability Outcome ***
16. Lintsen et al 2005	Smokers >1 cigarettes a day Non-smokers 0 cigarettes a day (self report)	Before oocyte retrieval	LB Delivery	Retrospective	8457	IVF	Single	Selection *** Comparability Outcome ***
17. Matalliotakis et al 2008b	Smokers vs Non-smokers (self report)	Before treatment	P Ultrasound scan	Retrospective	297	IVF,ICSI	Multiple	Selection *** Comparability * Outcome ***
18. Maximovich et al 1995	Smokers vs Non-smokers (self report)	Initial consultation	P Not specified	Retrospective	253	IVF	Multiple	Selection *** Comparability Outcome ***
19. Neal et al 2008	Smokers vs Non-smokers (self report)	Initial consultation	P Not specified	Prospective	29	IVF	Unclear	Selection * Comparability Outcome **

20. Pattinson et al 1991	Smokers >1 cigarettes a day Non-smokers 0 cigarettes a day (self report)	Initial consultation	LB Delivery	Retrospective	447	IVF	Single	Selection *** Comparability Outcome ***
21. Petanovski et al 2012	Smokers >1 cigarettes a day Non-smokers 0 cigarettes a day (self report)	Before oocyte retrieval	LB Delivery	Prospective	879	COS,ICSI	Single	Selection *** Comparability Outcome ***
22. Sharara et al 1994	Smokers vs Non-smokers (self report)	Timing not specified	LB Delivery	Retrospective	102	IVF	Unclear	Selection ** Comparability Outcome ***
23. Sterzik et al 1996	Smokers vs non-smokers (self report and - cotinine concentrations >50 ng/mL and non-smokers cotinine concentrations <=20 ng/mL)	Self report before and cotinine testing during treatment	P Ultrasound scan	Prospective	197	IVF	Single	Selection **** Comparability Outcome ***
24. Tiboni et al	Smokers >1 cigarettes a day Non-smokers 0	Timing not specified	P Ultrasound scan	Prospective	60	IVF,ICSI	Unclear	Selection *** Comparability

2004	cigarettes a day (self report)							Outcome ***
25. Trapp et al 1986	Smokers vs non-smokers(self-report and assessment of SCN concentrations (Rhodanide)	During treatment	P Pregnancy test	Prospective	114	IVF	Unclear	Selection ** Comparability Outcome **
26. Van Voorhis et al 1996	Smokers vs Non-smokers (self report)	Timing not specified	P Ultrasound scan	Retrospective	499	IVF, GIFT and ZIFT	Single	Selection *** Comparability Outcome ***
27. Weigert et al 1999	Smokers >1 cigarettes a day Non-smokers 0 cigarettes a day (self report)	Before stimulation	P Not specified	Retrospective	834	IVF	Unclear	Selection ** Comparability Outcome **
28. Wright et al 2006	Smokers >1 cigarettes a day Non-smokers 0 cigarettes a day (self report)	Initial consultation	P Ultrasound scan	Retrospective	389	IVF, ICSI	Single	Selection ** Comparability Outcome ***

Note: ART = Assisted reproductive technologies; GIFT = Gamete intra-fallopian transfer; ICSI = intracytoplasmic sperm injection; IVT = in vitro fertilisation; LB = live birth outcome data; ZIFT = zygote intrafallopian transfer. The sample size refers to data that is extracted from the papers and used in the meta-analysis.

Table 3: Study characteristics of Alcohol consumption studies

Authors	Variable/ classification	Time of assessment	Outcome & assessment of outcome	Design	Sample Size	Treatment	Cycle (single or multiple)	Newcastle-Ottawa Quality Score
1. Matalliotakis et al 2008b	Alcohol consumption vs non-alcohol consumption (self report)	Before treatment	P Ultrasound scan	Retrospective	297	IVF,ICSI	Multiple	Selection *** Comparability * Outcome ***
2. Rossi et al 2011	Alcohol drinkers >50 g (> 4 drinks per week) vs non-alcohol drinkers 0-49g(<4 drinkers per week) (self report)	Before treatment	LB Delivery	Prospective	4729 cycles	IVF	Multiple	Selection *** Comparability Outcome ***

Note: ART = Assisted reproductive technologies; ICSI = intracytoplasmic sperm injection; IVT = in vitro fertilisation; LB = live birth outcome data; P= pregnancy outcome data. The sample size refers to data that is extracted from the papers and used in the meta-analysis.

Table 4: Sensitivity analyses

BMI		
	OR [95% CI OR]	**Heterogeneity (I^2)**
Live birth only k=20	1.16 [1.07, 1.26], z=3.532, p=0.001	32.832%, p=0.078
Pregnancy only k=27	1.286 [1.125, 1.471], z=3.675, p=0.001	62.673%, p=0.001
Pregnancy scan only k=18	1.295 [1.117, 1.501] z=3.436, p=0.001	69.091%, p=0.001
Single cycle only k=23	1.167 [1.061, 1.284] z=3.186, p=0.001	34.046%, p=0.057
Only IVF k=10	1.385 [1.018, 1.885] z=2.071, p=0.038	79.358%, p=0.001
ICSI treatments k=3	1.261 [0.914, 1.739] z=1.412, p=0.158	81.952%, p=0.004
ICSI and IVF k=33	1.193 [1.108, 1.284] z=4.696, p<0.001	27.103%, p=0.078
Prospective studies k=10	1.216 [0.976, 1.516] z=1.740, p=0.082	45.114%, p=0.059
High quality studies k=10	1.284 [1.038, 1.587] z=2.305, p=0.021	72.451%, p<0.001
Recent studies only k=27	1.212 [1.078, 1.364] z=3.204, p=0.001	62.399%, p=0.001
SMOKING		
live birth outcomes k=10	1.510 [1.174, 1.942] z=3.206 p=0.001)	57.315%, p=0.012

pregnancy outcomes k=18	1.444 [1.121, 1.861] z=2.843: p=0.004)	51.317%, p=0.006
pregnancy scan only k = 13	1.373 [1.015-1.856] z=2.058: p=0.04:	51.328%, p =0.017
Single cycle k=17	1.623 [1.280, 2.057] z=3.998: p<0.001	65.000%, p<0.001
IVF only k=12	1.461 [1.194-1.787] z=3.686: p<0.001)	23.208%, p =0.216
IVF and ICSI mixed k=11:	1.430 [1.037-1.971] z=2.182: p=0.029:	62.836%, p=0.003
Prospective studies k=14	1.711 [1.247-2.348] z=3.327: p=0.001)	66.571%, p< 0.001
High quality study k=7)	1.416 [0.972, 2.065] z=1.811: p=0.070	67.440, p=0.005
Recent studies only k=10	1.548 [1.124-2.132] z=2.678: p=0.007:	66.902%, p =0.001

Note: *There was only two studies that reported only using ICSI in the smoking analysis and no studies which used a positive pregnancy test as an outcome so these sensitivity analyses are not presented*

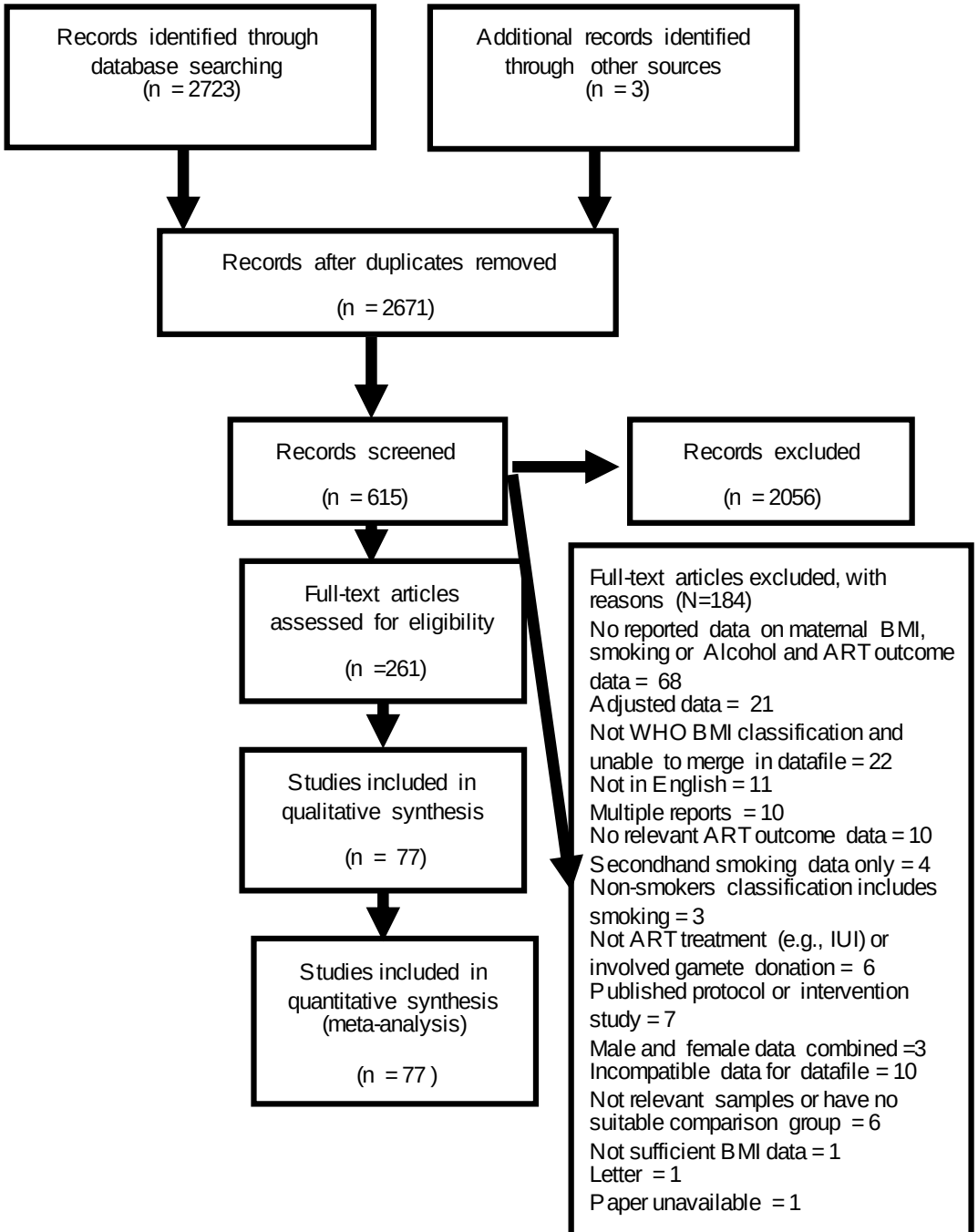
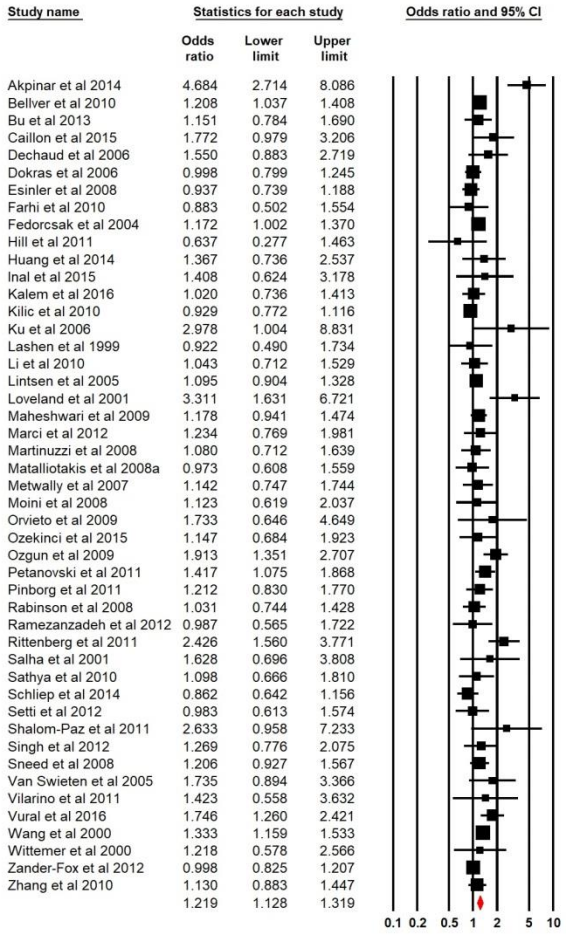
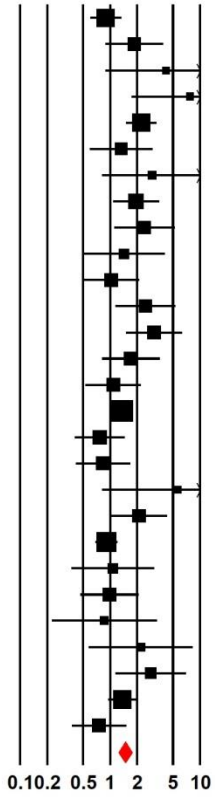
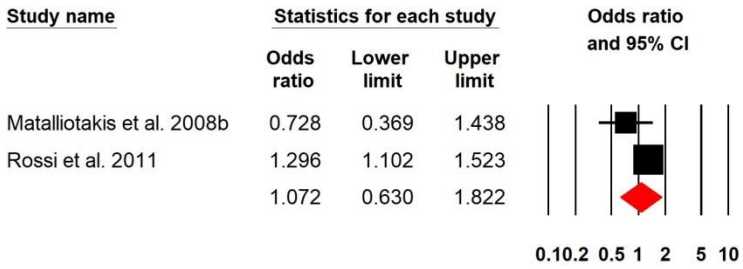

Records identified through database searching (n = 2723)
Additional records identified through other sources (n = 3)
Records after duplicates removed (n = 2671)
Records screened (n = 615)
Records excluded (n = 2056)
Full-text articles assessed for eligibility (n =261)
Full-text articles excluded, with reasons (N=184)
No reported data on maternal BMI, smoking or Alcohol and ART outcome data = 68
Adjusted data = 21
Not WHO BMI classification and unable to merge in datafile = 22
Not in English = 11
Multiple reports = 10
No relevant ART outcome data = 10
Secondhand smoking data only = 4
Non-smokers classification includes smoking = 3
Not ART treatment (e.g., IUI) or involved gamete donation = 6
Published protocol or intervention study = 7
Male and female data combined =3
Incompatible data for datafile = 10
Not relevant samples or have no suitable comparison group = 6
Not sufficient BMI data = 1
Letter = 1
Paper unavailable = 1
Studies included in qualitative synthesis (n = 77)
Studies included in quantitative synthesis (meta-analysis) (n = 77)

Figure 1: PRISMA 2009 Flow Diagram of studies included in the lifestyle and body mass index meta-analysis


Study name
Statistics for each study
Odds ratio and 95% CI
Odds ratio
Lower limit
Upper limit
Akpinar et al 2014 4.684 2.714 8.086
Bellver et al 2010 1.208 1.037 1.408
Bu et al 2013 1.151 0.784 1.690
Caillon et al 2015 1.772 0.979 3.206
Dechaud et al 2006 1.550 0.883 2.719
Dokras et al 2006 0.998 0.799 1.245
Esinler et al 2008 0.937 0.739 1.188
Farhi et al 2010 0.883 0.502 1.554
Fedorcsak et al 2004 1.172 1.002 1.370
Hill et al 2011 0.637 0.277 1.463
Huang et al 2014 1.367 0.736 2.537
Inal et al 2015 1.408 0.624 3.178
Kalem et al 2016 1.020 0.736 1.413
Kilic et al 2010 0.929 0.772 1.116
Ku et al 2006 2.978 1.004 8.831
Lashen et al 1999 0.922 0.490 1.734
Li et al 2010 1.043 0.712 1.529
Lintsen et al 2005 1.095 0.904 1.328
Loveland et al 2001 3.311 1.631 6.721
Maheshwari et al 2009 1.178 0.941 1.474
Marci et al 2012 1.234 0.769 1.981
Martinuzzi et al 2008 1.080 0.712 1.639
Matalliotakis et al 2008a 0.973 0.608 1.559
Metwally et al 2007 1.142 0.747 1.744
Moini et al 2008 1.123 0.619 2.037
Orvieto et al 2009 1.733 0.646 4.649
Ozekinci et al 2015 1.147 0.684 1.923
Ozgun et al 2009 1.913 1.351 2.707
Petanovski et al 2011 1.417 1.075 1.868
Pinborg et al 2011 1.212 0.830 1.770
Rabinson et al 2008 1.031 0.744 1.428
Ramezanzadeh et al 2012 0.987 0.565 1.722
Rittenberg et al 2011 2.426 1.560 3.771
Salha et al 2001 1.628 0.696 3.808
Sathya et al 2010 1.098 0.666 1.810
Schliep et al 2014 0.862 0.642 1.156
Setti et al 2012 0.983 0.613 1.574
Shalom-Paz et al 2011 2.633 0.958 7.233
Singh et al 2012 1.269 0.776 2.075
Sneed et al 2008 1.206 0.927 1.567
Van Swieten et al 2005 1.735 0.894 3.366
Vilarino et al 2011 1.423 0.558 3.632
Vural et al 2016 1.746 1.260 2.421
Wang et al 2000 1.333 1.159 1.533
Wittemer et al 2000 1.218 0.578 2.566
Zander-Fox et al 2012 0.998 0.825 1.207
Zhang et al 2010 1.130 0.883 1.447
1.219 1.128 1.319
0.1 0.2 0.5 1 2 5 10

Study name	Odds ratio	Lower limit	Upper limit
Al-Saleh et al. 2010	0.893	0.604	1.320
Ben-Haroush et al. 2011	1.853	0.896	3.833
Chung et al. 1997	4.198	0.888	19.858
Crha et al. 2001	7.719	1.734	34.358
Dessolle et al. 2011	2.221	1.519	3.247
El-Nemr et al. 1998	1.328	0.600	2.943
Freour et al 2013	2.923	0.813	10.515
Freour et al. 2010	1.940	1.082	3.478
Freour et al. 2012	2.403	1.115	5.180
Fuentes et al. 2010	1.426	0.504	4.040
Gruber et al. 2008	1.033	0.509	2.096
Hannoun et al. 2010	2.477	1.156	5.306
Harrison et al. 1990	3.095	1.518	6.307
Hughes et al. 1994	1.698	0.816	3.532
Joesbury et al. 1998	1.084	0.536	2.194
Lintsen et al. 2005	1.364	1.192	1.561
Matalliotakis et al. 2008b	0.765	0.404	1.447
Maximovich et al. 1995	0.834	0.418	1.666
Neal et al. 2008	5.683	0.819	39.426
Pattinson et al. 1991	2.096	1.035	4.248
Petanovski et al. 2012	0.907	0.683	1.204
Sharara et al. 1994	1.076	0.374	3.093
Sterzik et al. 1996	0.984	0.471	2.058
Tiboni et al. 2004	0.860	0.225	3.285
Trapp et al. 1986	2.188	0.578	8.273
Van Voorhis et al. 1996	2.822	1.146	6.952
Weigert et al. 1999	1.370	0.952	1.973
Wright et al. 2006	0.754	0.378	1.506
	1.457	1.228	1.727




Study name
Statistics for each study
Odds ratio
Lower limit
Upper limit
Odds ratio and 95% CI
Matalliotakis et al. 2008b 0.728 0.369 1.438
Rossi et al. 2011 1.296 1.102 1.523
1.072 0.630 1.822
0.1 0.2 0.5 1 2 5 10