Cardiovascular and metabolic profiles of offspring conceived by assisted reproductive technologies: a systematic review and meta-analysis

Xiao-Yan Guo, M.D.,[a] Xin-Mei Liu, Ph.D.,[b,c] Li Jin, Ph.D.,[b,c] Ting-Ting Wang, Ph.D.,[b,c] Kamran Ullah, Ph.D.,[d] Jian-Zhong Sheng, M.D., Ph.D.,[d] and He-Feng Huang, M.D.[a,b,c]

[a] Key Laboratory of Reproductive Genetics, Ministry of Education, Zhejiang University, Zhejiang; [b] International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University, Shanghai; [c] Institute of Embryo-Fetal Original Adult Disease, Affiliated to Shanghai Jiao Tong University, Shanghai; and [d] Department of Pathology and Pathophysiology, School of Medicine, Zhejiang University, Zhejiang, People's Republic of China

Objective: To evaluate cardiovascular and metabolic features of offspring conceived by in vitro fertilization/intracytoplasmic sperm injection (IVF-ICSI).
Design: Literature review and meta-analysis.
Setting: Not applicable.
Patient(s): Offspring from IVF-ICSI versus natural conception.
Intervention(s): None.
Main Outcome Measure(s): Systolic and diastolic blood pressure (SBP and DBP), cardiovascular function, body mass index (BMI), and lipid and glucose profiles.
Result(s): We included 19 studies that had recruited 2,112 IVF-ICSI and 4,096 naturally conceived offspring, ranging from childhood to early adulthood. The blood pressure levels of IVF-ICSI offspring were statistically significantly higher than those of naturally conceived offspring (weighted mean differences and confidence intervals: 1.88 mm Hg [95% CI, 0.27, 3.49] for SBP and 1.51 mm Hg [95% CI, 0.33, 2.70] for DBP). In addition, cardiac diastolic function was suboptimal and vessel thickness was higher among IVF-ICSI offspring. Compared with the metabolism of naturally conceived offspring, IVF-ICSI offspring displayed comparable BMI, lower low-density lipoprotein cholesterol levels, and higher fasting insulin levels.
Conclusion(s): Children conceived by IVF-ICSI manifested a minor yet statistically significant increase in blood pressure without the clustering of increased BMI or impaired lipid metabolism by early adulthood. Our findings indicate a risk of cardiovascular disease among IVF-ICSI offspring, which calls for longer-term follow-ups and further investigation. (Fertil Steril® 2017;107:622–31. ©2016 by American Society for Reproductive Medicine.)
Key Words: IVF, ICSI, blood pressure, BMI, metabolism

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/13964-22940

More than 5 million babies worldwide are born by in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (1). Thus, the potential health risks associated with these treatments are of great importance to public health. Inherent to IVF and ICSI treatments are numerous artificial procedures, including ovulation stimulation, manipulation of the oocyte and sperm, and embryo culture. These operations occur during gametogenesis and in early embryogenesis, a critical window for the establishment of genome methylation patterns (2, 3). According to the developmental origins of health and disease theory, the early epigenetic changes caused by assisted reproductive technology (ART) may lead to not only adverse perinatal outcomes (4–7) but also chronic cardiometabolic diseases in the latter stages of life (8–10).

Received August 17, 2016; revised and accepted December 8, 2016; published online January 16, 2017.
X.-Y.G. has nothing to disclose. X.-M.L. has nothing to disclose. L.J. has nothing to disclose. T.-T.W. has nothing to disclose. J.-Z.S. has nothing to disclose. H.-F.H. has nothing to disclose.
Supported by the National Natural Science Foundation of China (grant 81300545) and the National Basic Research Program of China (grant 2013CB967404).
Reprint requests: He-Feng Huang, M.D., International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200030, People's Republic of China (E-mail: huanghefg@hotmail.com).

Fertility and Sterility® Vol. 107, No. 3, March 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.12.007

Long-term cardiovascular and metabolic risks in IVF-ICSI offspring have gained increased attention in both animal models and human studies. In mice bred by ART, the following symptoms were documented: endothelial dysfunction and increased stiffness of the vasculature (11, 12), elevated systolic blood pressure (13, 14), altered glucose parameters (15, 16), and impaired activities of fatty acid metabolism-related enzymes (17). Similar to the animal data, the data from human studies has also indicated that ART offspring are prone to elevated blood pressure and impaired vascular function (18, 19) compared with their naturally conceived (NC) counterparts. In addition, ART offspring exhibited abnormal retinal vessel morphology (20), congenital heart defect (21), and different protein expression profiles in their umbilical veins (22). Furthermore, ART pregnancies were linked to preterm birth and low birth weight (5, 7), which are risk factors for future metabolic syndromes (23–25). Given these discoveries and the popularity of ART, a more comprehensive investigation of the cardiometabolic risk of ART offspring is necessary.

Despite the accumulating epidemiologic data, the conclusions are still preliminary and sometimes inconsistent. Studies on the individual effect of IVF and ICSI have been few. We took a combined approach and assessed the effect of these two techniques together to determine the cardiometabolic outcomes of the offspring. We summarize here the available clinical evidence on cardiometabolic parameters of IVF-ICSI offspring, including systolic and diastolic blood pressure (SBP and DBP), other cardiovascular functions, body mass index (BMI), lipid profiles (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglyceride), and glucose homeostasis variables (fasting serum glucose, fasting insulin, and homeostasis model of assessment for insulin resistance [HOMA-IR]).

MATERIALS AND METHODS

Search Strategy

An extensive literature search in PubMed and Scopus was last performed on October 1, 2016. We followed the PRISMA flow diagram to identify the studies (Supplemental Fig. 1, available online) based on the combinations of key terms in the following three categories. The first category was composed of "IVF, ICSI, ART, in vitro fertilization, assisted reproduction, assisted reproductive technology/technique, fertility treatment, cryopreservation, PGD, and preimplantation genetic diagnosis/screening." The second category consisted of "health, growth, outcome, physical, medical, phenotypic, development, blood pressure, hypertension, cardiac, vascular, metabolic, lipid, cholesterol, adiposity, body fat, BMI, obesity, glucose, insulin, and diabetes." The third category consisted of "cohort, follow up, case-control, children/childhood, adolescent/adolescence, puberty/pubertal, offspring, singleton, twin, adult, and postnatal."

A total of 1,911 articles were returned. After excluding irrelevant studies according to titles and abstracts, 37 full-text English clinical articles addressing the cardiovascular and metabolic profiles of IVF and ICSI offspring were obtained. Cross references of the included studies were manually searched for additional resources.

Selection Criteria

The literature selection process is detailed in Supplemental Table 1 (available online). The exclusion criteria were as follows: [1] studies that evaluated obstetric or perinatal events; [2] studies that did not evaluate the effects of IVF-ICSI but evaluated the effects of ovulation induction (26, 27) or preimplantation genetic diagnosis (PGD) (28); [3] no naturally conceived offspring as a comparison group (29–32); [4] overlapping subject groups (33–40) (in such cases, only the primary publication that had the highest study quality and provided the most information was selected for inclusion to prevent giving unreasonably larger weight to any study population when summarizing the data); and [5] studies with insufficient data (41–43). Additionally, three studies were excluded from the BMI analyses because they either lacked the standard deviation (44) or matched BMI as baseline (45, 46). The three studies, however, were still included in other analyses. Finally, among the 37 studies, 19 were included, which reported data on 2,112 IVF-ICSI offspring and 4,096 NC offspring.

Data Extraction and Quality Assessment

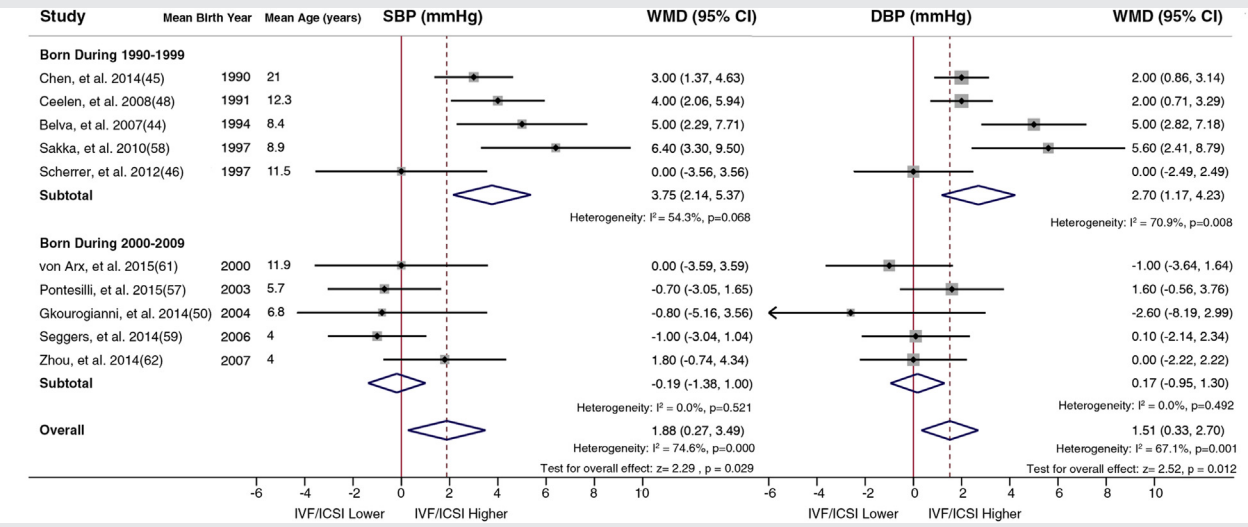
Basic study characteristics and main results were extracted by two independent reviewers and are presented in Supplemental Table 2 (available online) (44–62). We adapted the Newcastle-Ottawa quality assessment scale (63) to assess study quality, and the results are listed in Supplemental Table 3 (available online). In cases of uncertainty, a third author was consulted to reach a consensus. Study quality was considered high at 6–8 points, medium at 3–5 points, and low at 0–2 points.

Data Analysis

Meta analyses were performed on blood pressure, BMI, and metabolic parameters. Weighted mean differences (WMD) and 95% confidence intervals (CI) were calculated with inverse variance weighting. A random-effects model was used unless heterogeneity was low. In the latter case, a fixed-effect model was used instead. Heterogeneity between the studies was examined by chi-square tests for statistical significance. $P<.1$ was considered statistically significant. Inconsistency among studies was quantified using I-square tests, where I^2 values of $<25\%$ were considered low, 25% to 75% were considered moderate and $>75\%$ were considered high (64).

Substantial heterogeneity between studies was expected because the included studies recruited diverse study populations. First, the age of the study populations ranged from 1 year to 22 years. Concurrently, blood pressure, BMI, and metabolic profiles change dramatically from childhood to puberty to adulthood (65, 66). Second, the IVF-ICSI protocols have undergone major changes over the past years (67, 68). Therefore, the year of birth might reflect the development status of the IVF-ICSI technique and be a source of heterogeneity. Moreover, the plurality and conception mode of subjects, the choice of comparison group, study size, study

FIGURE 1



Systolic and diastolic blood pressure of 872 IVF-ICSI offspring versus 3,034 naturally conceived offspring. Studies are arranged and grouped by mean birth year of the children. Random effects model was used. CI = confidence interval; DBP = systolic diastolic blood pressure; SBP = systolic blood pressure; WMD = weighted mean difference.

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.

quality, study design, and geographic region all stood a chance of adding to the variance. To account for these effects, prespecified subgroup analyses were conducted to assess the heterogeneity. Differences among the subgroups were assessed using a restricted-maximum likelihood–based meta-regression.

Influence analysis was performed to test the robustness of the pooled estimates. Besides, a funnel plot with Egger's test was conducted to assess the risk of publication bias when 10 or more studies were included. All the statistical tests were two-sided and were performed in STATA 14.0 (StataCorp).

RESULTS

Blood Pressure

A random-effects meta-analysis of blood pressure was performed based on 10 studies, which recruited altogether 872 IVF-ICSI offspring and 3,034 NC offspring. Results showed a minor but statistically significant WMD between the blood pressure levels of IVF-ICSI offspring and those of NC offspring. Specifically, the SBP and DBP of IVF-ICSI offspring were 1.88 mm Hg (95% CI, 0.27, 3.49) and 1.52 mm Hg (95% CI, 0.34, 2.70) higher, respectively (Fig. 1).

However, high heterogeneity was observed (for SBP, I^2 = 74.6%, P=.001 and for DBP, I^2 = 67.1%, P=.001). To explore the potential sources of heterogeneity, subgroup analyses were performed on the study characteristics and participant characteristics, such as age and birth year of subjects, study size, and study quality. The results showed that heterogeneity was statistically significantly reduced by stratifying the birth year, but this effect was not observed in any other factors (data not shown). The IVF-ICSI offspring born during 1990–1999 exhibited a statistically significantly higher WMD of SBP than those born during 2000–2009 (3.75 mm Hg [95% CI, 2.14, 5.37] versus −0.186 mm Hg [95% CI, −1.38, 1.00], P=.006 between subgroups). The WMD of DBP was also statistically significantly higher in those born during 1990–1999 than in those born during 2000–2009 (2.70 mm Hg [95% CI, 2.14, 5.37] versus −0.19 [95% CI, −1.38, 1.00], P=.049 between subgroups).

To further investigate the impact of birth year on SBP, a restricted maximum likelihood–based meta-regression analysis was performed. The birth year category had a statistically significant regression coefficient for SBP (P=.006) and DBP (P=.049), which were not further improved by entering other covariates into the model. Between-study variance for SBP was reduced from 4.75 to 0.60, and the percentage explained by birth year category was 88.02%. For DBP, between-study variance was reduced from 2.18 to 1.50, and the percentage explained was 50.34%.

Considering that the 2000–2009 group also were younger and had a higher proportion of ICSI offspring, we further performed meta-regression analyses to evaluate the effect of age and ICSI proportion on WMD of blood pressure. The results showed that neither age nor ICSI proportion could explain the between-study variance (data not shown). In other words, the improvement in blood pressure manifested by IVF-ICSI offspring over the years was not because of biases introduced by younger participants or a larger ICSI proportion.

Funnel plot of SBP and DBP showed a nearly symmetrical scattering and the results of Egger's test were not statistically significant (P=.640 and P=.501), suggesting the absence of publication bias. Additionally, influence analyses were performed by omitting one study at a time and recalculating the overall effect size to identify potential outliers and

TABLE 1

Heart and vascular function of 402 IVF-ICSI offspring versus those of 382 naturally conceived offspring.

Study	No. in study	Mean age	Main findings (IVF-ICSI offspring versus naturally conceived offspring)
Valenzuela-Alcaraz et al. 2013 (60)	60 IVF-ICSI vs. 75 NC	1 mo	Vascular wall thickness: [1] Aortic maximum intima-media thickness 0.65 (0.62–0.66) mm vs. 0.57 (0.47–0.64) mm, $P<.01$. [2] Carotid maximum intima-media thickness 0.32 (0.31–0.33) mm vs. 0.29 (0.20–0.33) mm, $P<.01$.
	50 IVF-ICSI vs. 50 NC	6 mo	Cardiac diastolic function: [1] Mitral E deceleration time 63 (49–78) ms vs. 66 (52–90) ms, $P<.05$. [2] Tricuspid E deceleration time 52 (44–66) ms vs. 62 (51–77) ms, $P<.001$. [3] Left isovolumic relaxation time 63 (55–67) ms vs. 50 (41–59) ms, $P<.001$.
			Vascular wall thickness: [1] Aortic maximum intima-media thickness 0.72 (0.68–0.75) mm vs. 0.60 (0.52–0.64) mm, $P<.01$.
Zhou et al. 2014 (62)	128 IVF-ICSI vs. 100 NC	4 y	Geometric morphology: [1] Left ventricular mass index 55.70 (15.14) g/m^2 vs. 49.73 (9.78) g/m^2, $P<.01$. [2] Left ventricular remodeling index 0.86 (0.20) g/mL vs. 0.80 (0.14) m/mL, $P<.01$.
			Cardiac diastolic function: [1] Mitral A, ventricular inflow during atrial contraction 59.51 (14.91) mm/s vs. 65.56 (15.75) mm/s, $P<.01$. [2] Mitral E′ 9.66 (1.52) mm/s vs. 10.13 (1.76) mm/s, $P<.01$.
Liu et al. 2015 (55)	100 IVF vs. 100 NC	5 y	Cardiac diastolic function: [1] Tricuspid E deceleration time 128.36 (18.74) ms vs. 141.58 (19.55) ms, $P<.05$. [2] Left isovolumic relaxation time 77.46 (6.84) ms vs. 68.20 (6.55) ms, $P<.05$.
von Arx et al. 2015 (61)	54 IVF-ICSI vs. 54 NC	11.9 y	At low altitude, cardiac morphometry and function were not different. Under the stressful conditions of high-altitude-induced pressure overload and hypoxia: [1] Right ventricular end-diastolic area 17.9 (3.9) cm^2 vs. 15.7 (2.9) cm^2, $P<.01$. [2] Tricuspid E′ 16.8 (2.8) cm/s vs. 19.2 (2.2) cm/s, $P<.001$.
Scherrer et al. 2012 (46)	60 IVF-ICSI vs. 53 NC	12 y	Systemic vascular function: [1] Flow-mediated dilation of the brachial artery 6.7 (1.6) % vs. 8.6 (1.7) %, $P<.0001$. [2] Pulse-wave velocity 7.8 (2.4) m/s vs. 6.5 (1.3) m/s, $P<.001$. [3] Carotid intima-media thickness 410 (30) μm vs. 370 (20) μm, $P<.0001$.
			Pulmonary vascular function: [1] Pulmonary artery pressure at high altitude 39 (11) mm Hg vs. 30 (9) mm Hg, $P<.0001$.

Note: Studies were arranged by the age of subjects. E = ventricular inflow in early diastole; E′ = annular peak velocity in early diastole; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization.

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.

influential cases (Supplemental Fig. 2, available online). When each of four studies was omitted (44, 45, 48, 58), the 95% CI of the weighted mean difference of SBP and DBP became −0.16, 3.58 and −0.03, 2.86, respectively, indicating that the blood pressure of IVF-ICSI offspring would no longer be statistically significantly higher than that of NC offspring. Such results suggested that the overall effect size was small and would be affected when studies with positive effect estimates were omitted.

Cardiovascular Function

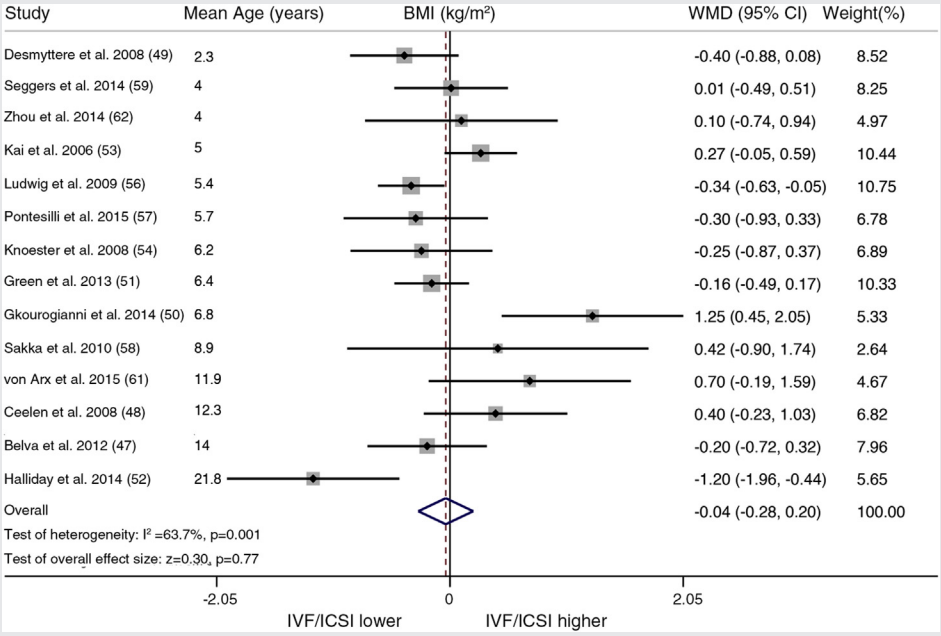
Table 1 presents five studies that measured cardiovascular morphology and function of 402 IVF-ICSI offspring versus 382 NC offspring by echocardiographic recording. These studies included relatively young subjects at various developmental stages and studied different aspects of cardiovascular function. No meta-analysis was performed in this section because the number of studies was limited. A suboptimal cardiac diastolic function was consistently reported in the IVF-ICSI group, especially under stressful conditions such as high altitude. Furthermore, two studies claimed statistically significantly higher aortic and carotid intima-media thickness in IVF-ICSI offspring.

Adiposity

Fourteen studies reported BMI, for 1,914 IVF-ICSI offspring and 3,881 NC participants in total. Other adiposity measures were also reported, such as total body fat percentage, waist circumference, and skin-fold thickness (53). Because these measures were not available in most studies, they were not included in our meta-analysis.

No statistically significant difference of BMI was found between IVF-ICSI and NC offspring (−0.04 kg/m^2 [95% CI, −0.28, 0.20]) (Fig. 2). Given that heterogeneity was statistically significant (I^2 = 63.7%, P=.001), we performed subgroup analyses. The results showed that heterogeneity

FIGURE 2



Body mass index of 1,914 IVF-ICSI offspring versus 3,881 naturally conceived offspring. Studies are arranged according to mean age of the subjects. Random effects model was used. CI = confidence interval; WMD = weighted mean difference.

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.

would be statistically significantly reduced when the two low-quality studies (50, 52) were excluded (I^2 = 34.1%, P=.12), with no influence on the overall mean difference (−0.06 kg/m^2 [95% CI, −0.24, 0.12]). Heterogeneity remained high for other subgroup analyses (data not shown), indicating that low study quality was the main source of variance in BMI.

The funnel plot of BMI was not skewed, and the result of Egger's test was not statistically significant (P=.43), suggesting no publication bias. The influence analysis showed that no single study statistically significantly affected the pooled estimate (95% CI, −0.13, 0.10).

Glucose and Lipid Metabolism

In total, seven studies addressed the glucose profiles of 477 IVF-ICSI offspring and 1,852 NC offspring (Fig. 3). The fasting insulin of the IVF-ICSI offspring was statistically significantly higher (0.38 mIU/L [95% CI, 0.08, 0.68]). However, fasting glucose and HOMA-IR were comparable (−0.03 mM [95% CI, −0.13, 0.06] and 0.02 [95% CI, −0.06, 0.12], respectively). High heterogeneity was detected throughout these three glucose metabolism markers, but we did not perform a subgroup analysis due to the limited number of studies.

For the lipid profiles, five studies assessed various aspects of lipid metabolism in 332 IVF-ICSI offspring and 1,701 NC offspring (Fig. 3). The IVF-ICSI offspring had statistically significantly lower LDL cholesterol (−0.10 mM [95% CI, −0.19, −0.01]) while their HDL cholesterol, total cholesterol, triglycerides were comparable (0.02 mM [95% CI, −0.02, 0.07]; −0.04 mM [95% CI, −0.14, 0.07]; and −0.06 [95% CI, −0.13, 0.02], respectively). Heterogeneity was low except for triglycerides.

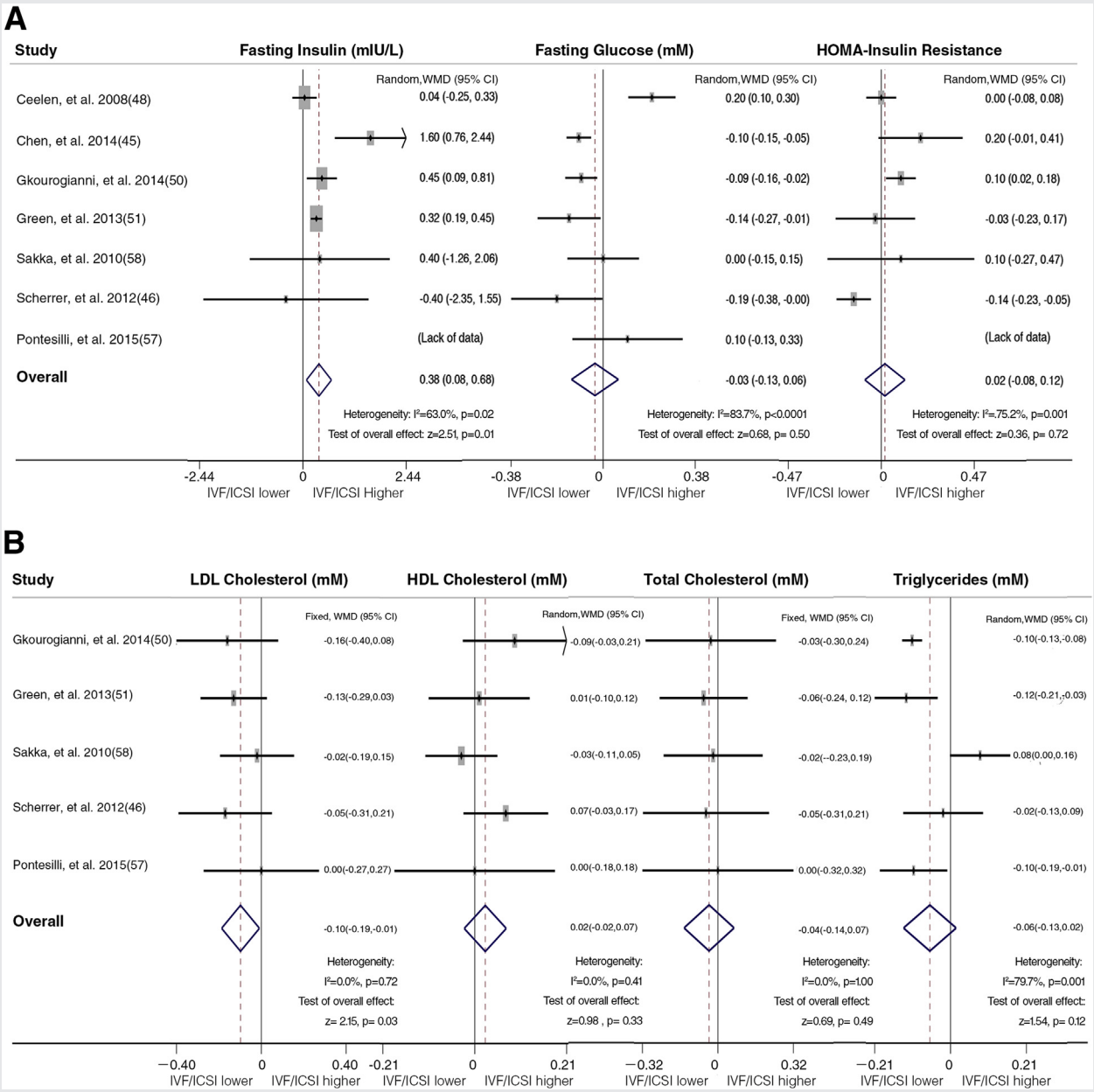
DISCUSSION

The present review included existing data from 19 studies which investigated 2,112 IVF-ICSI offspring and 4,096 NC offspring with regard to their blood pressure, cardiovascular function, adiposity, and metabolism during childhood, puberty, and early adulthood. A minor yet significant increase in blood pressure was observed in IVF-ICSI offspring when compared with naturally conceived offspring. Besides, the cardiac diastolic function was suboptimal, and the vessel thickness was higher among IVF-ICSI offspring. However, the potential cardiovascular risk was not clustered by increased BMI or impaired lipid metabolism. Our findings indicated the risk of cardiovascular diseases among IVF-ICSI offspring, which called for longer-term follow-ups and further investigations.

Biological and Clinical Significance

An important question is raised as whether such small difference in blood pressure during childhood and adolescence would track into adulthood and increase the risk of hypertension. Clinical data supported that the natural history of hypertension could be traced back to elevated blood pressure in childhood (69–73). On a population level, even a minor decrement in adult SBP as small as 2 mm Hg in adult SBP can translate into a 6% cutdown in the prevalence of stroke, a 4% decrease in coronary heart disease, and a 3% reduction in overall mortality (74, 75). Therefore, the

FIGURE 3



(**A**) Glucose homeostasis variables and (**B**) lipid profiles of 477 IVF-ICSI offspring versus 1,852 naturally conceived offspring. Studies are arranged by first author. Random or fixed effects model was used according to the heterogeneity. CI = confidence interval; HDL = high-density lipoprotein; HOMA = homeostasis model of assessment; LDL = low-density lipoprotein; WMD = weighted mean difference.

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.

clinical importance of the minimal increase in blood pressure detected in this meta-analysis should not be underestimated, especially in the presence of consistent changes in vessel thickness and diastolic function.

Another interesting finding was that the birth year of IVF-ICSI offspring played an important role in their blood pressure. The IVF-ICSI children born during 1990–1999 had SBP levels that were 4 mm Hg higher than the NC children born during the same corresponding period. However, IVF-ICSI offspring born during 2000–2009 had SBP levels comparable with their NC counterparts. Further analysis by meta-regression indicated that an earlier birth year was correlated with a higher WMD in SBP, and this effect was independent of age or ICSI proportion. One possible explanation would be the maturation of IVF-ICSI techniques over the years. In particular, ovulation induction protocols, in vitro culture conditions, the number of embryos transferred, the advent of ICSI, and the efficiency of ART therapies have all

made substantial progress over time (67, 68). As a result, perinatal outcomes have been improved, and the birth defect rate has been reduced markedly over the last two decades among both IVF-ICSI singletons and twins (76–78). It is also reasonable to suggest that the blood pressure of IVF-ICSI offspring may have improved accordingly.

The parameters of lipid and glucose metabolism did not show consistent differences. The IVF-ICSI children presented with statistically significantly lower LDL cholesterol, with a trend for lower total cholesterol, lower triglycerides, and higher HDL cholesterol (although not statistically significant), indicating a probably more favorable lipid profile. At the same time, the fasting insulin level was statistically significantly higher in the IVF-ICSI offspring but not the fasting glucose or HOMA-IR.

To facilitate the early detection of potential abnormalities, we looked for more sensitive metabolic markers. Retinol-binding protein 4 (RBP-4) and neutrophil gelatinase-associated lipocalin (NGAL) are two such markers, which would elevate in the serum before the manifestation of frank diabetes. Sakka et al. (39) reported that IVF children had statistically significantly higher circulating RBP-4 and NGAL levels, suggesting early glucose derangements. However, the data on metabolic profiles are still preliminary at present, so further studies are needed before we can draw a prudent conclusion.

Strengths and Limitations

Ours is the first meta-analysis to quantify the cardiovascular and metabolic indices of IVF-ICSI offspring. To our knowledge, the existing reviews (18, 19, 79) failed to do an exhaustive literature search and focused only on a subset of the available literature. Moreover, they only described or listed data in tables without performing quantitative analysis.

Nevertheless, our meta-analysis has some important limitations that are common in this type of study. First, statistically significant heterogeneity was present in most of the analyses. This is not surprising because the included studies investigated diverse populations with varied age groups and conception modes. In addition, the choices between fertile and subfertile parents for the comparison group were different. However, the results of subgroup analyses and meta-regressions showed that none of these confounding factors statistically significantly affected the results (data not shown).

Second, the results were limited by the lack of original individual-level data. We could not stratify our blood pressure results by gender, infertility type, diet, or exercise level, which could be important confounders. Besides, although the adjusted blood pressure percentiles (66) and the incidence of prehypertension, hypertension, prediabetes, and diabetes would provide valuable information, they were not reported by most studies. Third, the results of influence analyses showed that the pooled effect sizes of SBP and DBP were minimal and relied on studies with positive effect estimates (44, 45, 48, 58), so the results of blood pressure should be considered with an appropriate degree of caution.

Potential Causes and Mechanisms of Elevated Blood Pressure

Current opinions favor a lifelong perspective for understanding the etiology of chronic noncommunicable diseases, believing that adult-onset diseases can be traced back to their gamete and embryo-fetal origins (80). These diseases are integrative consequences of genetic and epigenetic inheritance, coupled with epigenetic changes caused by developmental and environmental influences (81). We propose that the elevated blood pressure of IVF-ICSI offspring may be attributed to four major factors that exert intertwined effects: parental subfertility, ART procedures, intrauterine environment, and adult lifestyle choices.

Parental background. Couples who receive ART treatment are likely to be subfertile, be older, or have genetic diseases, all of which imply an aberrant maturation process of sperms and oocytes and carry a higher risk of transmitting chromatin abnormality, DNA damage, or incorrect methylation patterns to the offspring (82–84). In an attempt to minimize the confounding role of the parental infertility background, Ceelen et al. and Seggers et al. (48, 59) set the comparison group as naturally conceived singletons born to subfertile couples instead of fertile couples. These two studies gave discrepant results with regard to the blood pressure levels of IVF-ICSI offspring, so the effect of parental infertility requires further investigation.

ART procedures. Epigenetic and genetic changes associated with ART are convincingly observed in humans and animal models (85–89). The methylation patterns at CpG sites of the ART offspring were different from those of NC offspring, which was true for both imprinting and nonimprinting genes, including those that regulate glucose and lipid metabolism (90–93).

Among all the technical details of ART, the side effects of ovarian stimulation have been the most studied (94). Ovulation induction induces significant endocrine changes to foster multiple follicular maturation and corpus lutea development, which may disrupt downstream processes such as oocyte maturation, implantation, and early pregnancy (83, 89). High maternal estrogen levels after ovulation induction are associated with elevated total cholesterol and LDL-C levels in newborns (95). Notably, a study found that children born to women who had ovarian hyperstimulation syndrome (OHSS) displayed reduced systolic and diastolic functions in their common carotid arteries compared with those whose mothers underwent IVF without OHSS and children who were naturally conceived (27). In accordance, Seggers et al. (59) discovered that IVF with controlled ovarian hyperstimulation would lead to statistically significantly higher SBP in offspring than modified natural cycles.

Intrauterine environment. The importance of intrauterine environment can never be overemphasized because it acts as a transducer of the current environment during the critical window of development. A plethora of data have indicated that a suboptimal maternal diet (96–98), stress (99, 100), and hormonal state during pregnancy influence the developmental programing of the next generation. Women

receiving ART treatments are potentially exposed to not only endocrine challenges but also advanced maternal age, chronic pelvic inflammation, insulin resistance secondary to polycystic ovary syndrome, autoimmune disease, and even chemotherapy (101). The fact that IVF-ICSI offspring are more susceptible to low birth weight and preterm birth might partly stem from a compromised in utero environment.

Adult lifestyle choices. As is well known, lifestyle greatly affects the risk of hypertension (102). Therefore, exercise level, eating habits, and alcohol and tobacco consumption among IVF-ICSI children are important factors that must be considered. Little is known, however, about the lifestyle choices of this population or the effect of those choices on the developmental programing of hypertension.

Unanswered Questions and Future Research

Several issues have yet to be fully answered. First, is the minor blood pressure elevation in young IVF-ICSI offspring an indicator of a higher risk of future hypertension? Second, how do we disentangle the respective roles of the ART technique, the cause of parental infertility, and the neonatal factors on any future cardiometabolic parameters? Third, how do we identify the individual risk of a specific technical factor so that we can achieve technical refinements and improve the overall outcome? Fourth, can epigenetic modifications associated with cardiometabolic diseases be corrected by lifestyle modifications, or will they be passed on to future generations?

New ART procedures have been introduced such as preimplantation genetic diagnosis, low-cost IVF, and artificial gametes (103–105). Besides, the application of IVF-ICSI is not limited to infertile couples; it also extends to other fields such as fertility preservation in cancer patients. These trends entail the necessity to confirm the long-term safety of ART.

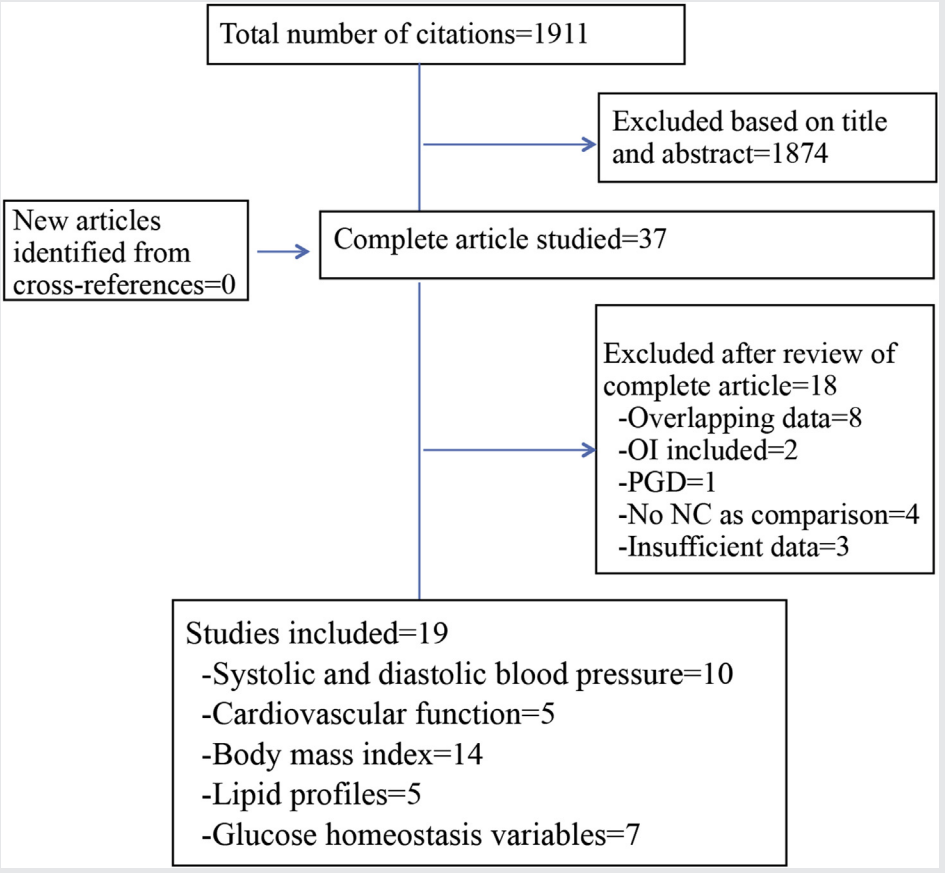
REFERENCES

1. Kissin DM, Jamieson DJ, Barfield WD. Monitoring health outcomes of assisted reproductive technology. New Engl J Med 2014;371:91–3.
2. Reik W. Stability and flexibility of epigenetic gene regulation in mammalian development. Nature 2007;447:425–32.
3. Feil R, Fraga MF. Epigenetics and the environment: emerging patterns and implications. Nat Rev Genet 2012;13:97–109.
4. Niakan KK, Han J, Pedersen RA, Simon C, Pera RA. Human preimplantation embryo development. Development 2012;139:829–41.
5. Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjærven R, Gunnell D, et al. Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. Lancet 2008;372:737–43.
6. Hansen M, Kurinczuk JJ, Milne E, de Klerk N, Bower C. Assisted reproductive technology and birth defects: a systematic review and meta-analysis. Hum Reprod Update 2013;19:330–53.
7. Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Söderström-Anttila V, et al. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. Hum Reprod Update 2013;19:87–104.
8. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ 1989;298:564–7.
9. Barker DJ. The origins of the developmental origins theory. J Intern Med 2007;261:412–7.
10. Morton JS, Cooke CL, Davidge ST. In utero origins of hypertension: mechanisms and targets for therapy. Physiol Rev 2016;96:549–603.
11. Rexhaj E, Paoloni-Giacobino A, Rimoldi SF, Fuster DG, Anderegg M, Somm E, et al. Mice generated by in vitro fertilization exhibit vascular dysfunction and shortened life span. J Clin Invest 2013;123:5052–60.
12. Schenewerk AL, Ramírez FÍ, Foote C, Ji T, Martínez-Lemus LA, Rivera RM. Effects of the use of assisted reproduction and high-caloric diet consumption on body weight and cardiovascular health of juvenile mouse offspring. Reproduction 2014;147:111–23.
13. Watkins AJ, Platt D, Papenbrock T, Wilkins A, Eckert JJ, Wing YK, et al. Mouse embryo culture induces changes in postnatal phenotype including raised systolic blood pressure. Proc Natl Acad Sci USA 2007;104:5449–54.
14. Rexhaj E, Pireva A, Paoloni-Giacobino A, Allemann Y, Cerny D, Dessen P, et al. Prevention of vascular dysfunction and arterial hypertension in mice generated by assisted reproductive technologies by addition of melatonin to culture media. Am J Physiol Heart Circ Physiol 2015;309:H1151–6.
15. Scott KA, Yamazaki Y, Yamamoto M, Lin Y, Melhorn SJ, Krause EG, et al. Glucose parameters are altered in mouse offspring produced by assisted reproductive technologies and somatic cell nuclear transfer. Biol Reprod 2010;83:220–7.
16. Donjacour A, Liu X, Lin W, Simbulan R, Rinaudo PF. In vitro fertilization affects growth and glucose metabolism in a sex-specific manner in an outbred mouse model. Biol Reprod 2014;90:80.
17. Wang LY, Le F, Wang N, Li L, Liu XZ, Zheng YM, et al. Alteration of fatty acid metabolism in the liver, adipose tissue, and testis of male mice conceived through assisted reproductive technologies: fatty acid metabolism in ART mice. Lipids Health Dis 2013;12:5.
18. Yeung EH, Druschel C. Cardiometabolic health of children conceived by assisted reproductive technologies. Fertil Steril 2013;99:318–26.e4.
19. Scherrer U, Rexhaj E, Allemann Y, Sartori C, Rimoldi SF. Cardiovascular dysfunction in children conceived by assisted reproductive technologies. Eur Heart J 2015;36:1583–9.
20. Wikstrand MH, Niklasson A, Strömland K, Hellström A. Abnormal vessel morphology in boys born after intracytoplasmic sperm injection. Acta Paediatr 2008;97:1512–7.
21. Padhee M, Zhang S, Lie S, Wang KC, Botting KJ, Caroline McMillen I, et al. The periconceptional environment and cardiovascular disease: Does in vitro embryo culture and transfer influence cardiovascular development and health? Nutrients 2015;7:1378–425.
22. Gao Q, Pan HT, Lin XH, Zhang JY, Jiang Y, Tian S, et al. Altered protein expression profiles in umbilical veins: insights into vascular dysfunctions of the children born after in vitro fertilization. Biol Reprod 2014;91:71.
23. Johansson S, Iliadou A, Bergvall N, Tuvemo T, Norman M, Cnattingius S. Risk of high blood pressure among young men increases with the degree of immaturity at birth. Circulation 2005;112:3430–6.
24. Kaijser M, Bonamy AK, Akre O, Cnattingius S, Granath F, Norman M, et al. Perinatal risk factors for ischemic heart disease: Disentangling the roles of birth weight and preterm birth. Circulation 2008;117:405–10.
25. De Jong F, Monuteaux MC, Van Elburg RM, Gillman MW, Belfort MB. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. Hypertension 2012;59:226–34.
26. Bay B, Mortensen EL, Kesmodel US. Is subfertility or fertility treatment associated with long-term growth in the offspring? A cohort study. Fertil Steril 2014;102:1117–23.
27. Xu GF, Zhang JY, Pan HT, Tian S, Liu ME, Yu TT, et al. Cardiovascular dysfunction in offspring of ovarian-hyperstimulated women and effects of estradiol and progesterone: a retrospective cohort study and proteomics analysis. J Clin Endocrinol Metab 2014;99:E2494–503.
28. Seggers J, Haadsma ML, Bastide-Van Gemert SL, Heineman MJ, Kok JH, Middelburg KJ, et al. Blood pressure and anthropometrics of 4-y-old children born after preimplantation genetic screening: Follow-up of a unique, moderately sized, randomized controlled trial. Pediatr Res 2013;74:606–14.
29. Bouillon C, Leandri R, Desch L, Ernst A, Bruno C, Cerf C, et al. Does embryo culture medium influence the health and development of children born after in vitro fertilization? PLoS One 2016;11:e0150857.
30. Desmyttere S, Bonduelle M, Nekkebroeck J, Roelants M, Liebaers I, De Schepper J. Growth and health outcome of 102 2-year-old children

conceived after preimplantation genetic diagnosis or screening. Early Hum Dev 2009;85:755–9.
31. Wennerholm UB, Bonduelle M, Sutcliffe A, Bergh C, Niklasson A, Tarlatzis B, et al. Paternal sperm concentration and growth and cognitive development in children born with a gestational age more than 32 weeks after assisted reproductive therapy. Hum Reprod 2006;21:1514–20.
32. Foix-L'Helias L, Grynberg M, Ducot B, Frydman N, Kerbrat V, Bouyer J, et al. Growth development of French children born after in vitro maturation. PLoS One 2014;9:e89713.
33. Belva F, Painter R, Bonduelle M, Roelants M, Devroey P, De Schepper J. Are ICSI adolescents at risk for increased adiposity? Hum Reprod 2012;27:257–64.
34. Belva F, Roelants M, Painter R, Bonduelle M, Devroey P, De Schepper J. Pubertal development in ICSI children. Hum Reprod 2012;27:1156–61.
35. Ceelen M, Van Weissenbruch MM, Roos JC, Vermeiden JP, Van Leeuwen FE, Delemarre-van De Waal HA. Body composition in children and adolescents born after in vitro fertilization or spontaneous conception. J Clin Endocrinol Metab 2007;92:3417–23.
36. Ceelen M, Van Weissenbruch MM, Vermeiden JPW, Van Leeuwen FE, Delemarre-Van De Waal HA. Pubertal development in children and adolescents born after IVF and spontaneous conception. Hum Reprod 2008;23:2791–8.
37. Ceelen M, Van Weissenbruch MM, Prein J, Smit JJ, Vermeiden JP, Spreeuwenberg M, et al. Growth during infancy and early childhood in relation to blood pressure and body fat measures at age 8–18 years of IVF children and spontaneously conceived controls born to subfertile parents. Hum Reprod 2009;24:2788–95.
38. Miles HL, Hofman PL, Peek J, Harris M, Wilson D, Robinson EM, et al. In vitro fertilization improves childhood growth and metabolism. J Clin Endocrinol Metab 2007;92:3441–5.
39. Sakka SD, Margeli A, Loutradis D, Chrousos GP, Papassotiriou I, Kanaka-Gantenbein C. Gender dimorphic increase in RBP-4 and NGAL in children born after IVF: an epigenetic phenomenon? Eur J Clin Invest 2013;43:439–48.
40. Rimoldi SF, Sartori C, Rexhaj E, Bailey DM, Marchi SF, McEneny J, et al. Antioxidants improve vascular function in children conceived by assisted reproductive technologies: a randomized double-blind placebo-controlled trial. Eur J Prev Cardiol 2015;22:1399–407.
41. Beydoun HA, Sicignano N, Beydoun MA, Matson DO, Bocca S, Stadtmauer L, et al. A cross-sectional evaluation of the first cohort of young adults conceived by in vitro fertilization in the United States. Fertil Steril 2010;94:2043–9.
42. Beydoun HA, Sicignano N, Beydoun MA, Bocca S, Stadtmauer L, Oehninger S. Pubertal development of the first cohort of young adults conceived by in vitro fertilization in the United States. Fertil Steril 2011;95:528–33.
43. Bonduelle M, Bergh C, Niklasson A, Palermo GD, Wennerholm UB, Collaborative Study Group B. Medical follow-up study of 5-year-old ICSI children. Reprod Biomed Online 2004;9:91–101.
44. Belva F, Henriet S, Liebaers I, Van Steirteghem A, Celestin-Westreich S, Bonduelle M. Medical outcome of 8-year-old singleton ICSI children (born ≥32 weeks' gestation) and a spontaneously conceived comparison group. Hum Reprod 2007;22:506–15.
45. Chen M, Wu L, Zhao J, Wu F, Davies MJ, Wittert GA, et al. Altered glucose metabolism in mouse and humans conceived by IVF. Diabetes 2014;63:3189–98.
46. Scherrer U, Rimoldi SF, Rexhaj E, Stuber T, Duplain H, Garcin S, et al. Systemic and pulmonary vascular dysfunction in children conceived by assisted reproductive technologies. Circulation 2012;125:1890–6.
47. Belva F, Roelants M, De Schepper J, Roseboom TJ, Bonduelle M, Devroey P, et al. Blood pressure in ICSI-conceived adolescents. Hum Reprod 2012;27:3100–8.
48. Ceelen M, van Weissenbruch MM, Vermeiden JP, van Leeuwen FE, Delemarre-van de Waal HA. Cardiometabolic differences in children born after in vitro fertilization: follow-up study. J Clin Endocrinol Metab 2008;93:1682–8.
49. Desmyttere S, De Schepper J, Nekkebroeck J, De Vos A, De Rycke M, Staessen C, et al. Two-year auxological and medical outcome of singletons born after embryo biopsy applied in preimplantation genetic diagnosis or preimplantation genetic screening. Hum Reprod 2009;24:470–6.
50. Gkourogianni A, Kosteria I, Telonis AG, Margeli A, Mantzou E, Konsta M, et al. Plasma metabolomic profiling suggests early indications for predisposition to latent insulin resistance in children conceived by ICSI. PLoS One 2014;9:e94001.
51. Green MP, Mouat F, Miles HL, Hopkins SA, Derraik JG, Hofman PL, et al. Phenotypic differences in children conceived from fresh and thawed embryos in in vitro fertilization compared with naturally conceived children. Fertil Steril 2013;99:1898–904.
52. Halliday J, Wilson C, Hammarberg K, Doyle LW, Bruinsma F, McLachlan R, et al. Comparing indicators of health and development of singleton young adults conceived with and without assisted reproductive technology. Fertil Steril 2014;101:1055–63.
53. Kai CM, Main KM, Andersen AN, Loft A, Chellakooty M, Skakkebæk NE, et al. Serum insulin-like growth factor-I (IGF-I) and growth in children born after assisted reproduction. J Clin Endocrinol Metab 2006;91:4352–60.
54. Knoester M, Helmerhorst FM, Vandenbroucke JP, van der Westerlaken LA, Walther FJ, Veen S. Perinatal outcome, health, growth, and medical care utilization of 5- to 8-year-old intracytoplasmic sperm injection singletons. Fertil Steril 2008;89:1133–46.
55. Liu H, Zhang Y, Gu HT, Feng QL, Liu JY, Zhou J, et al. Association between assisted reproductive technology and cardiac alteration at age 5 years. JAMA Pediatr 2015;169:603–5.
56. Ludwig AK, Katalinic A, Thyen U, Sutcliffe AG, Diedrich K, Ludwig M. Physical health at 5.5 years of age of term-born singletons after intracytoplasmic sperm injection: results of a prospective, controlled, single-blinded study. Fertil Steril 2009;91:115–24.
57. Pontesilli M, Painter RC, Grooten IJ, Van Der Post JA, Mol BW, Vrijkotte TG, et al. Subfertility and assisted reproduction techniques are associated with poorer cardiometabolic profiles in childhood. Reprod Biomed Online 2015;30:258–67.
58. Sakka SD, Loutradis D, Kanaka-Gantenbein C, Margeli A, Papastamataki M, Papassotiriou I, et al. Absence of insulin resistance and low-grade inflammation despite early metabolic syndrome manifestations in children born after in vitro fertilization. Fertil Steril 2010;94:1693–9.
59. Seggers J, Haadsma ML, La Bastide-Van Gemert S, Heineman MJ, Middelburg KJ, Roseboom TJ, et al. Is ovarian hyperstimulation associated with higher blood pressure in 4-year-old IVF offspring? Part I: multivariable regression analysis. Hum Reprod 2014;29:502–9.
60. Valenzuela-Alcaraz B, Crispi F, Bijnens B, Cruz-Lemini M, Creus M, Sitges M, et al. Assisted reproductive technologies are associated with cardiovascular remodeling in utero that persists postnatally. Circulation 2013;128:1442–50.
61. Von Arx R, Allemann Y, Sartori C, Rexhaj E, Cerny D, de Marchi SF, et al. Right ventricular dysfunction in children and adolescents conceived by assisted reproductive technologies. J Appl Physiol 2015;118:1200–6.
62. Zhou J, Liu H, Gu HT, Cui YG, Zhao NN, Chen J, et al. Association of cardiac development with assisted reproductive technology in childhood: a prospective single-blind pilot study. Cell Physiol Biochem 2014;34:988–1000.
63. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
64. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. Chichester, United Kingdom: John Wiley & Sons; 2009.
65. Hickman TB, Briefel RR, Carroll MD, Rifkind BM, Cleeman JI, Maurer KR, et al. Distributions and trends of serum lipid levels among United States children and adolescents ages 4–19 years: data from the Third National Health and Nutrition Examination Survey. Prev Med 1998;27:879–90.
66. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004;114:555–76.

67. Wang J, Sauer MV. In vitro fertilization (IVF): a review of 3 decades of clinical innovation and technological advancement. Ther Clin Risk Manag 2006;2:355–64.
68. Boulet SL, Mehta A, Kissin DM, Warner L, Kawwass JF, Jamieson DJ. Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection. JAMA 2015;313:255–63.
69. Law CM, De Swiet M, Osmond C, Fayers PM, Barker DJP, Cruddas AM, et al. Initiation of hypertension in utero and its amplification throughout life. BMJ 1992;306:24–7.
70. Srinivasan SR, Myers L, Berenson GS. Changes in metabolic syndrome variables since childhood in prehypertensive and hypertensive subjects: the Bogalusa Heart Study. Hypertension 2006;48:33–9.
71. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 2008;117:3171–80.
72. Rademacher ER, Jacobs DR Jr, Moran A, Steinberger J, Prineas RJ, Sinaiko A. Relation of blood pressure and body mass index during childhood to cardiovascular risk factor levels in young adults. J Hypertens 2009;27:1766–74.
73. Morrison JA, Glueck CJ, Wang P. Childhood risk factors predict cardiovascular disease, impaired fasting glucose plus type 2 diabetes mellitus, and high blood pressure 26 years later at a mean age of 38 years: the Princeton-lipid research clinics follow-up study. Metabolism 2012;61:531–41.
74. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, et al. Primary prevention of hypertension: clinical and public health advisory from the National High Blood Pressure Education Program. JAMA 2002;288:1882–8.
75. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. Implications of small reductions in diastolic blood pressure for primary prevention. Arch Intern Med 1995;155:701–9.
76. Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Otterblad Olausson P. Trends in delivery and neonatal outcome after in vitro fertilization in Sweden: data for 25 years. Hum Reprod 2010;25:1026–34.
77. Hansen M, Kurinczuk JJ, de Klerk N, Burton P, Bower C. Assisted reproductive technology and major birth defects in Western Australia. Obstet Gynecol 2012;120:852–63.
78. Henningsen AA, Gissler M, Skjaerven R, Bergh C, Tiitinen A, Romundstad LB, et al. Trends in perinatal health after assisted reproduction: a Nordic study from the CoNARTaS group. Hum Reprod 2015;30:710–6.
79. Hart R, Norman RJ. The longer-term health outcomes for children born as a result of IVF treatment: Part I—general health outcomes. Hum Reprod Update 2013;19:232–43.
80. Zhu YM, Hu XL, Wu YT, Feng C, Huang HF. Assisted reproductive technology and gamete/embryo-fetal origins of diseases. In: Huang HF, Sheng JZ, editors. Gamete and embryo-fetal origins of adult diseases. Dordrecht, the Netherlands: Springer; 2014:197–219.
81. Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev 2014;94:1027–76.
82. Kobayashi H, Sato A, Otsu E, Hiura H, Tomatsu C, Utsunomiya T, et al. Aberrant DNA methylation of imprinted loci in sperm from oligospermic patients. Hum Mol Genet 2007;16:2542–51.
83. Khoueiry R, Ibala-Rhomdane S, Mery L, Blachere T, Guerin JF, Lornage J, et al. Dynamic CpG methylation of the KCNQ1OT1 gene during maturation of human oocytes. J Med Genet 2008;45:583–8.
84. Aitken RJ, Curry BJ. Redox regulation of human sperm function: from the physiological control of sperm capacitation to the etiology of infertility and DNA damage in the germ line. Antioxid Redox Signal 2011;14:367–81.
85. London SN, Young D, Caldito G, Mailhes JB. Clomiphene citrate-induced perturbations during meiotic maturation and cytogenetic abnormalities in mouse oocytes in vivo and in vitro. Fertil Steril 2000;73:620–6.
86. Delimitreva S, Zhivkova R, Isachenko E, Umland N, Nayudu PL. Meiotic abnormalities in in vitro-matured marmoset monkey (*Callithrix jacchus*) oocytes: development of a non-human primate model to investigate causal factors. Hum Reprod 2006;21:240–7.
87. Feng C, Wang LQ, Dong MY, Huang HF. Assisted reproductive technology may increase clinical mutation detection in male offspring. Fertil Steril 2008;90:92–6.
88. Katari S, Turan N, Bibikova M, Erinle O, Chalian R, Foster M, et al. DNA methylation and gene expression differences in children conceived in vitro or in vivo. Hum Mol Genet 2009;18:3769–78.
89. Van Montfoort AP, Hanssen LL, De Sutter P, Viville S, Geraedts JP, De Boer P. Assisted reproduction treatment and epigenetic inheritance. Hum Reprod Update 2012;18:171–97.
90. Olofsson LE, Orho-Melander M, William-Olsson L, Sjoholm K, Sjostrom L, Groop L, et al. CCAAT/enhancer binding protein alpha (C/EBPα) in adipose tissue regulates genes in lipid and glucose metabolism and a genetic variation in C/EBPα is associated with serum levels of triglycerides. J Clin Endocrinol Metab 2008;93:4880–6.
91. Feng C, Tian S, Zhang Y, He J, Zhu XM, Zhang D, et al. General imprinting status is stable in assisted reproduction-conceived offspring. Fertil Steril 2011;96:1417–23.e9.
92. Whitelaw N, Bhattacharya S, Hoad G, Horgan GW, Hamilton M, Haggarty P. Epigenetic status in the offspring of spontaneous and assisted conception. Hum Reprod 2014;29:1452–8.
93. Vincent RN, Gooding LD, Louie K, Chan Wong E, Ma S. Altered DNA methylation and expression of PLAGL1 in cord blood from assisted reproductive technology pregnancies compared with natural conceptions. Fertil Steril 2016;106:739–48.e3.
94. de Waal E, Yamazaki Y, Ingale P, Bartolomei MS, Yanagimachi R, McCarrey JR. Gonadotropin stimulation contributes to an increased incidence of epimutations in ICSI-derived mice. Hum Mol Genet 2012;21:4460–72.
95. Meng Y, Lv PP, Ding GL, Yu TT, Liu Y, Shen Y, et al. High maternal serum estradiol levels induce dyslipidemia in human newborns via a hepatic HMGCR estrogen response element. Sci Rep 2015;5:10086.
96. Roseboom T, de Rooij S, Painter R. The Dutch famine and its long-term consequences for adult health. Early Hum Dev 2006;82:485–91.
97. Watkins AJ, Lucas ES, Torrens C, Cleal JK, Green L, Osmond C, et al. Maternal low-protein diet during mouse pre-implantation development induces vascular dysfunction and altered renin-angiotensin-system homeostasis in the offspring. Br J Nutr 2010;103:1762–70.
98. van Uitert EM, Steegers-Theunissen RP. Influence of maternal folate status on human fetal growth parameters. Mol Nutr Food Res 2013;57:582–95.
99. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. Nat Neurosci 2004;7:847–54.
100. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 2008;3:97–106.
101. Hart RJ. Physiological aspects of female fertility: role of the environment, modern lifestyle, and genetics. Physiol Rev 2016;96:873–909.
102. Arena R, Guazzi M, Lianov L, Whitsel L, Berra K, Lavie CJ, et al. Healthy lifestyle interventions to combat noncommunicable disease-a novel nonhierarchical connectivity model for key stakeholders: a policy statement from the American Heart Association, European Society of Cardiology, European Association for Cardiovascular Prevention and Rehabilitation, and American College of Preventive Medicine. Eur Heart J 2015;36:2097–109.
103. Banerjee I, Shevlin M, Taranissi M, Thornhill A, Abdalla H, Ozturk O, et al. Health of children conceived after preimplantation genetic diagnosis: a preliminary outcome study. Reprod Biomed Online 2008;16:376–81.
104. Hendriks S, Dancet EA, van Pelt AM, Hamer G, Repping S. Artificial gametes: a systematic review of biological progress towards clinical application. Hum Reprod Update 2015;21:285–96.
105. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Hum Reprod Update 2015;21:411–26.

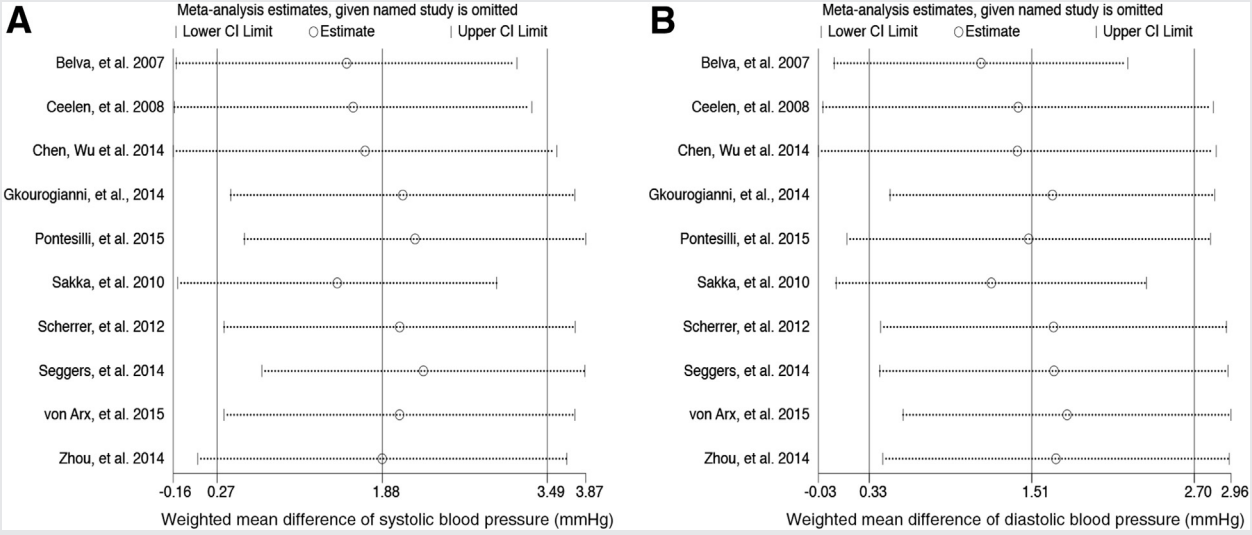
SUPPLEMENTAL FIGURE 1



PRISMA flowchart of literature search process. NC = naturally conceived offspring; OI = ovulation induction; PGD = preimplantation genetic diagnosis.

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 2



Influence analyses of (**A**) systolic blood pressure and (**B**) diastolic blood pressure. CI = confidence interval.

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.

SUPPLEMENTAL TABLE 1

Cardiovascular and metabolic profiles in ART offspring: literature search and selection.

Data source	PubMed, Scopus, Web of Science	
Search strategy	All combinations of key words in the three pertinent categories.	
Search key words	Category 1: IVF, ICSI, ART, in vitro fertilization, assisted reproduction, assisted reproductive technology/technique, fertility treatment, cryopreservation, PGD, preimplantation genetic diagnosis/screening Category 2: health, growth, outcome, physical, medical, phenotypic, development, blood pressure, hypertension, cardiac, vascular, metabolic, lipid, cholesterol, adiposity, body fat, BMI, obesity, glucose, insulin, diabetes Category 3: cohort, follow up, case-control, children/childhood, adolescent/adolescence, puberty/pubertal, offspring, singleton, twin, adult, postnatal	
Other sources	Cross-references	
Last search	October 1, 2016	
Exclusion criteria	Overlapping data	Belva et al. 2007 (44, ✓, included for blood pressure analysis) and Belva et al. 2012 (47, ✓, included for body mass index analysis) overlap with Belva et al. 2012 (33) and Belva et al. 2012 (34) Ceelen et al. 2008 (48, ✓) overlaps with Ceelen et al. 2007 (35), 2008 (36), 2009 (37) Green et al. 2013 (51, ✓) overlaps with Miles et al. 2007 (38) Scherrer et al. 2012 (46, ✓) overlaps with Rimoldi et al. 2015 (40) Sakka et al. 2010 (58, ✓) overlaps with Sakka et al. 2013 (39)
	No naturally conceived group as comparison	Bouillon et al. 2016 (29), Desmyttere et al. 2009 (30), Wennerholm et al. 2006 (31), Foix-L'Helias et al. 2014 (32)
	Insufficient data	Beydoun et al. 2010 (41), 2011 (42); Bonduelle et al. 2004 (43)
	Ovulation induction instead of IVF-ICSI	Bay et al. 2014 (26), Xu et al. 2014 (27)
	Preimplantation genetic diagnosis instead of IVF-ICSI	Seggers et al. 2013 (28)
Method for assessing data	A structured data extraction and evaluation sheet was applied as in Supplemental Tables 2 and 3	

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.

SUPPLEMENTAL TABLE 2

Cardiovascular and metabolic profiles in ART offspring: basic characteristics of the included studies.

Study	Country	Study design[a]	Groups[b]	Mean age (y)	Mean year of birth	Twins[c]	Birth weight[d]	Gestational age[d]	Maternal age[d]	Quality score[e]
Belva et al. 2007 (44)	Belgium	P	150 ICSI vs. 147 NC	8.4	1994	S	→	→	↑	7
Belva et al. 2012 (47)	Belgium	P	217 ICSI vs. 223 NC	14	1996	S	↓	↓	↑	5
Ceelen et al. 2008 (48)	Netherlands	R	225 IVF vs. 225 subfertile NC	12.3	1991	S	↓	↓	/	4
Chen et al. 2014 (45)	Australia	R	14 IVF vs. 20 NC	21	1990	S	/	/	/	1
Desmyttere et al. 2009 (49)	Belgium	P	70 ICSI vs. 69 NC	2.3	2004	S	→	→	↑	5
Gkourogianni et al. 2014 (50)	Athens	R	42 ICSI vs. 42 NC	6.8	2004	S&T	↓	↓	↑	1
Green et al. 2013 (51)	New Zealand	R	115 IVF-ICSI vs. 94 NC	6.4	1999	S	↓	→	↑	4
Halliday et al. 2014 (52)	Australia	R	547 IVF-ICSI vs. 549 NC	21.8	1987	S	↓	↓	↑	1
Kai et al. 2006 (53)	Denmark	P	135 IVF-ICSI vs. 70 NC	5	2002	S&T	↓	↓	↑	4
Knoester et al. 2008 (54)	Netherlands	R	165 IVF-ICSI vs. 85 NC	6.2	1998	S	↓	↓	↑	4
Liu et al. 2015 (55)	China	R	100 IVF vs. 100 NC	5	2007	S	→	→	→	6
Ludwig et al. 2009 (56)	German	P	276 ICSI vs. 273 NC	5.4	2000	S	↓	↓	↑	4
Pontesilli et al. 2015 (57)	Netherlands	P	28 IVF-ICSI vs. 2,244 NC	5.7	2003	S	→	→	↑	4
Sakka et al. 2010 (58)	Greece	R	106 IVF vs. 68 NC	8.9	1997	S&T	↓	↓	↑	3
Scherrer et al. 2012 (46)	Switzerland	R	65 IVF-ICSI vs. 57 NC	11.5	1997	S	→	→	↑	3
Seggers et al. 2014 (59)	Netherlands	P	115 IVF-ICSI vs. 79 subfertile NC	4	2006	S	↓	→	→	6
Valenzuela-Alcaraz et al. 2013 (60)	Spain	P	100 IVF-ICSI vs. 100 NC	0.5	2009	S	↓	↓	→	4
Von Arx et al. 2015 (61)	Switzerland	R	54 IVF-ICSI vs. 54 NC	11.9	2000	S	→	→	↑	4
Zhou et al. 2014 (62)	China	P	128 IVF-ICSI vs. 100 NC	4	2007	S&T	↓	↓	/	3

Note: ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization.
[a] P = prospective cohort; R = retrospective cohort.
[b] NC = naturally conceived offspring; subfertile NC = naturally conceived offspring by subfertile parents.
[c] S = singletons only; S&T = twins included.
[d] → =IVF-ICSI offspring are comparable with NC group; ↑=IVF-ICSI offspring higher; ↓=IVF-ICSI offspring lower; /=not mentioned.
[e] Quality scores were assessed by the adapted Newcastle-Ottawa Quality Assessment Scale (Supplemental Table 2).

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.

SUPPLEMENTAL TABLE 3

Cardiovascular and metabolic profiles in ART offspring: quality assessment of included studies by adapted Newcastle-Ottawa Quality Assessment Scale.

					Comparable parameters				Quality[e]	
Study	Sample size (≥100 ART offspring)	Study design[a]	Recruitment of controls[b]	Limited participation bias	Baseline[c]	Parental age, BMI, smoking, education	Birth weight and gestational age	Reliable outcome measures[d]	Score	Rating
Belva et al. 2007 (44)	1	1	1	1	1	0	1	1	7	High
Belva et al. 2012 (47)	1	1	1	1	0	0	0	1	5	Medium
Ceelen et al. 2008 (48)	1	0	1	1	1	0	0	0	4	Medium
Chen et al. 2014 (45)	0	0	0	0	1	0	0	0	1	Low
Desmyttere et al. 2009 (49)	0	1	0	1	1	0	1	1	5	Medium
Gkourogianni et al. 2014 (50)	0	0	0	0	0	0	0	1	1	Low
Green et al. 2013 (51)	1	0	1	1	1	0	0	0	4	Medium
Halliday et al. 2014 (52)	1	0	0	0	0	0	0	0	1	Low
Kai et al. 2006 (53)	1	1	0	1	0	0	0	1	4	Medium
Knoester et al. 2008 (54)	1	0	1	0	1	0	0	1	4	Medium
Liu et al. 2015 (55)	1	0	1	0	1	1	1	1	6	High
Ludwig et al. 2009 (56)	1	1	0	0	1	0	0	1	4	Medium
Pontesilli et al. 2015 (57)	0	1	1	0	1	0	1	0	4	Medium
Sakka et al. 2010 (58)	1	0	0	1	0	0	0	1	3	Medium
Scherrer et al. 2012 (46)	0	0	0	0	1	0	1	1	3	Medium
Seggers et al. 2014 (59)	1	1	0	1	1	1	0	1	6	High
Valenzuela-Alcaraz et al. 2013 (60)	1	1	0	0	1	1	0	0	4	Medium
Von Arx et al. 2015 (61)	0	0	1	0	1	0	1	1	4	Medium
Zhou et al. 2014 (62)	1	1	0	0	0	0	0	1	3	Medium

Note: ART = assisted reproduction technology; BMI = body mass index.

[a] Prospective/retrospective cohort.

[b] From the same source as ART offspring.

[c] Age, gender, twins, Tanner stage.

[d] By the same person, blinded.

[e] Low: 0–2; Medium: 3–5; high: 6–8.

Guo. Cardiometabolic profile of ART offspring. Fertil Steril 2016.