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ORIGINAL ARTICLE

Maternal blood leptin concentration in small for gestational age: a meta-analysis

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Abstract

Monitoring leptin concentration in maternal blood would be useful for earlier identification of mothers at risk of delivering small for gestational age (SGA) neonates. This study was performed to examine whether maternal blood leptin concentrations are different between SGA neonates and healthy controls. Meta-analysis was performed to summarize the data of all English-language studies providing the numbers of SGA neonates, the numbers of healthy controls, and the means and standard deviations of maternal blood leptin concentrations in these two groups. The studies were collected by searching ten databases including PubMed (MEDLINE) and investigating the PubMed Related Citations and bibliographic references. The Newcastle–Ottawa Scale was used to assess study quality. Publication bias was assessed using Egger's test. The primary outcome of this study was the standardized mean difference (SMD) in maternal blood leptin concentration between SGA neonates and healthy controls. Thirty-two overall good-quality studies involving 1734 women and their neonates were extracted from 17 articles. Synthetic evidence did not indicate statistically significant SMD in maternal blood leptin concentration between SGA neonates and healthy controls ($P = 0.172$). Egger's test showed no publication bias ($P = 0.309$).

Conclusion: Maternal blood leptin concentration is not significantly different between SGA neonates and healthy controls.

What is Known:
- *Monitoring leptin concentration in maternal blood would be useful for earlier identification of mothers at risk of delivering small for gestational age (SGA) neonates.*

What is New:
- *The results of this meta-analysis including 1734 women and their neonates in 32 overall good-quality studies showed that maternal blood leptin concentration is not significantly different between SGA neonates and healthy controls.*

Keywords Blood · Leptin · Meta-analysis · Mothers · Pregnancy · Small for gestational age

Abbreviations

CM	Congenital malformations
ELISA	Enzyme-linked immunosorbent assay
IRMA	Immunoradiometric assay
IUGR	Intrauterine growth restriction
NOS	Newcastle–Ottawa Scale
PE	Preeclampsia
RIA	Radioimmunoassay
SD	Standard deviation
SGA	Small for gestational age
SMD	Standardized mean difference

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Introduction

Similar to intrauterine growth restriction (IUGR), small for gestational age (SGA) is associated with perinatal mortality and morbidity [11, 25, 28, 31]. SGA neonates may also develop cardiovascular and metabolic diseases (complications of adipose tissue dysfunction) in later life [4, 23, 25]. Adipose tissue secretes biologically active molecules including leptin, but leptin is also produced by the placenta in humans [4, 23]. In addition to the regulation of hunger and satiety, leptin plays

important roles in fetal growth. For example, leptin may be involved in fetal organogenesis, i.e., maturation of the heart, brain, kidneys, and pancreas [4]. In addition, a meta-analysis indicated that cord leptin concentration is low in SGA compared to appropriate for gestational age [24]. On the other hand, placental hypoxia due to failure to remodel maternal arteries supplying the placenta, which results in IUGR, may trigger placental leptin production [5, 23]. This is compatible with some reports indicating that mothers with IUGR have a slightly large fraction of fat mass combined with high blood leptin concentration compared to those without IUGR [9, 23].

Monitoring leptin concentration in maternal blood would be more useful than in cord blood for earlier identification of mothers at risk of delivering SGA neonates. However, differences in maternal blood leptin concentration between SGA neonates and healthy controls are still controversial [4, 23]. Here, a meta-analysis was performed to examine whether maternal blood leptin concentrations are different between SGA neonates and healthy controls.

Materials and methods

Primary outcome and selection criteria

The primary outcome of this study was the standardized mean difference (SMD) [6] in maternal blood leptin concentration between SGA neonates and healthy controls. SGA was defined as birthweight below a centile value (e.g., 3rd, 5th, 10th, and 15th centile) for gestational age. There was no limitation regarding whether birthweight was measured at birth or estimated by ultrasound before birth. The inclusion criteria were all English-language studies that provided the numbers of SGA neonates, the numbers of healthy controls, the means and standard deviations (SDs) of maternal blood leptin concentrations in SGA neonates, and the means and SDs of maternal blood leptin concentrations in healthy controls.

Search strategies, study selection, and data extraction

PubMed (MEDLINE) was searched using the terms (February 26, 2018): ("small for gestational age" OR "small-for-gestational-age" OR "light for gestational age" OR light-for-gestational-age OR "small for date" OR small-for-date OR "small for dates" OR small-for-dates OR "light for date" OR light-for-date OR "light for dates" OR light-for-dates OR "intrauterine growth restriction" OR "intrauterine-growth-restriction" OR "intra uterine growth restriction" OR "intra-uterine growth restriction" OR "intra-uterine-growth-restriction" OR "intrauterine growth retardation" OR "intrauterine-growth-retardation" OR "intra uterine growth retardation" OR "intra-uterine growth retardation" OR "intra-uterine-growth-retardation" OR "fetal growth restriction" OR "fetal-growth-restriction" OR "fetal growth retardation" OR "fetal-growth-retardation") AND leptin AND (blood OR serum OR plasma) AND (mother OR mothers OR woman OR women OR maternal). There were no restrictions regarding publication date. Article titles and abstracts were scanned, and those that were determined to be unrelated were excluded. The full texts of the remaining articles were retrieved. Articles determined to be unrelated by retrieving the full texts were excluded. The remaining articles were finally eligible for inclusion in the analysis. The following strategies were added to locate additional articles, the full texts of which had to be retrieved. First, the PubMed Related Citations that were shown by clicking the "See all…" tab at the right side of the screen displaying each finally eligible article and the bibliographic references of the finally eligible articles were investigated. Second, nine other databases, i.e., CINAHL, PsycINFO, Wiley Online Library, ProQuest Central (e.g., ProQuest Health and Medical Complete and ProQuest Nursing & Allied Health Source), ProQuest Dissertations & Theses Global, the entire Cochrane Library (e.g., CENTRAL), Web of Knowledge, Google Scholar, and Sage Publication Online, were searched. The literature search was repeated periodically. Duplicated articles were integrated. The numbers of SGA neonates, the numbers of healthy controls, the means and SDs of maternal blood leptin concentration in SGA neonates, and the means and SDs of maternal blood leptin concentration in healthy controls were extracted.

Study quality assessment

The Newcastle–Ottawa Scale (NOS) consisting of eight questions to evaluate selection bias, comparability bias, exposure bias, and outcome bias in cohort or case–control studies [32] was used to assess study quality. Study quality was assessed five times, and the most frequent responses were regarded as the final responses. A "yes" response was assigned one star, and the NOS score was defined as the total number of stars for each study. One of eight questions in the NOS could provide two answers, and therefore the maximum NOS score was 9. NOS scores between 5 and 9 were deemed to indicate good-quality studies.

Statistical analysis

Stata/MP 13.1 (StataCorp LP, College Station, TX) was used for statistical analyses. Heterogeneity was assessed using I^2. Attempts were made to achieve homogeneity (i.e., $I^2 < 50\%$) from heterogeneous data (i.e., $I^2 \geq 50\%$) by selecting the studies. This selection was dependent on the following: (a) population characteristics, i.e., excluding vs. including preeclampsia (PE), excluding vs. including congenital malformations (CM), or excluding PE or CM vs, including PE and CM; (b) study location, i.e., each country vs. other countries, Africa, Asia, Europe, Latin America, the Middle East, North America, or

Oceania vs. other regions, or developing vs. developed countries; (c) study characteristics, i.e., cohort vs. case–control study, prospective vs. retrospective data collection, or NOS score ≥ 7 vs. < 7; (d) leptin measurement, i.e., blood sampling in 33 weeks or later vs. 32 weeks or earlier, or enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or immunoradiometric assay (IRMA) vs. others; (e) method of SGA diagnosis, i.e., actual birthweight vs. ultrasound estimation; or (f) cut-off point of SGA, i.e., 10th or 15th centile vs. 3rd or 5th centile (investigation of heterogeneity sources). The SMDs in maternal blood leptin concentration between SGA neonates and healthy controls were estimated using Hedge's g and then summarized [10]. The homogenous data were summarized using a fixed effects model (i.e., inverse variance method), and the heterogeneous data were summarized using a random effects model (i.e., the DerSimonian and Laird method).

The data were also summarized by selecting the studies in the same way as described for investigation of heterogeneity sources (subgroup analysis). The statistical significance of differences in the SMDs was evaluated between subgroups and their counterparts categorized in the same way as described for investigation of heterogeneity sources and subgroup analysis (meta-regression analysis). The variability in the results by exclusion of each one of the studies from the meta-analysis was evaluated (sensitivity analysis). Publication bias was assessed using Egger's test (publication bias assessment) [7].

Results

Systematic review

Seventeen articles were finally eligible for the analysis (Table 1 and Supplementary Fig. 1) [1–3, 5, 9, 12, 13, 16–19, 21, 22, 26, 30, 33, 34]. More than one study was sometimes extracted from one article, because some presented data from more than one population or blood sample taken at more than one time point. Therefore, 32 studies involving 1734 women and their neonates were extracted from these 17 articles to evaluate the difference in maternal blood leptin concentration between SGA neonates and healthy controls (Tables 1 and 2). Studies were conducted in three developing and six developed countries in Asia, Europe, the Middle East, and North America (Table 1). NOS scores were ≥ 5 in all of the studies, except for one study conducted by Lepercq et al. [18], suggesting the inclusion of overall good-quality studies.

Investigation of heterogeneity sources and meta-analysis

The SMDs of maternal blood leptin concentration between SGA neonates and healthy controls were summarized from the heterogeneous data in the total population ($I^2 = 61.8\%$) (Table 2) [1–3, 5, 9, 12, 13, 16–19, 21, 22, 26, 30, 33, 34]. Therefore, attempts were made to achieve homogeneity by limiting studies. Excluding reduction of the number of studies to two, the attempts that successfully achieved homogeneity were dependent on limitation to the USA [5, 13, 17, 30], North America [5, 13, 17, 30], cohort studies [9, 12, 19, 26, 30], RIA [5, 13, 16–19, 22, 26, 30, 33], IRMA [1, 9, 12], cut-off point by actual birthweight [2, 3, 5, 9, 12, 13, 16–19, 22, 26, 30], and blood sampling at 32 weeks or earlier [5, 30] (n = 17, 17, 18, 25, 3, 27, and 7, respectively).

In the total population, there was no statistically significant difference in maternal blood leptin concentration between SGA neonates and healthy controls ($n = 32$, $P = 0.172$) (Table 2 and Fig. 1) [1–3, 5, 9, 12, 13, 16–19, 21, 22, 26, 30, 33, 34].

Subgroup, meta-regression, and sensitivity analysis and publication bias assessment

Excluding reduction of the number of studies to two, the SMD value was not different between SGA neonates and healthy controls (n = 3–28, P = 0.051–0.989) in any subgroup except for cohort studies ($n = 18$, $P = 0.002$) [9, 12, 19, 26, 30] and cut-off point of 3rd or 5th centile ($n = 4$, $P = 0.010$) (Table 2) [2, 16, 26]. A cut-off point of 10th or 15th centile vs. 3rd or 5th centile was potentially a confounder based on an effect on the SMD value ($P = 0.027$). The differences in maternal blood leptin concentrations between SGA neonates and healthy controls did not vary after exclusion of each one of the studies from the analysis. No publication bias was detected in the data used to evaluate the differences in maternal blood leptin concentration between SGA neonates and healthy controls (P = 0.309) (Supplementary Fig. 2) [7, 29].

Discussion

Main findings

This is the first meta-analysis to evaluate the differences in maternal blood leptin concentration between SGA neonates and healthy controls. The synthetic evidence suggested that there is no statistically significant difference in maternal blood leptin concentration between SGA neonates and healthy controls. The findings of the present study were based on 32 studies involving 1734 women and their neonates in nine developing and developed countries in Asia, Europe, the Middle East, and North America [1–3, 5, 9, 12, 13, 16–19, 21, 22, 26, 30, 33, 34]. Therefore, the findings in the total population are generalizable (external validity). The findings of the present study were also based on the inclusion of overall good-quality studies, as indicated by NOS scores ≥ 5 for almost all of the included studies (Table 1). Therefore, the findings in the total

population were unlikely to have been affected by serious bias (internal validity).

Interpretations

Interpretation of the results was unlikely to be seriously affected by heterogeneity sources, confounders, and publication bias. The SMD changed to show a significant increase in maternal blood leptin concentration in SGA neonates compared to healthy controls by eliminating one of the heterogeneity sources, i.e., limiting to cohort studies (Table 2) [9, 12, 19, 26, 30]. However, this change may have been at least partly due to poor compatibility of data in cohort studies between SGA neonates and healthy controls compared to case–control studies, as indicated by the lower rate of studies that controlled for the most important factor

Table 1 Characteristics of included studies

Author (year)	Country	Design	Exclusion Criteria	NOS Score	Leptin Kit	Time	SGA Cut-off point	Method
Arslan (2004)	Turkey	Case–control	CM	5	IRMA	At birth	10th centile	Ultrasound
Aydin (2014)	Turkey	Case–control	PE; CM	6	ELISA	Predelivery	3rd centile	Actual weight
Aydin (2016)	Turkey	Case–control	PE; CM	8	ELISA	At birth	10th centile	Actual weight
Catov (a) (2007)	USA	Case–control	PE	7	RIA	18 wks	10th centile	Actual weight
Catov (b) (2007)	USA	Case–control	PE	7	RIA	28 wks	10th centile	Actual weight
Catov (c) (2007)	USA	Case–control	PE	7	RIA	Predelivery	10th centile	Actual weight
Ferrero (2015)	Spain	Cohort	PE; CM	7	IRMA	32–34 wks	10th centile	Actual weight
Grisau-Granovsky (2003)	Israel	Cohort	PE	8	IRMA	At birth	10th centile	Actual weight
Jenkins (2007)	USA	Case–control	PE	6	RIA	At admission for birth	10th centile	Actual weight
Kyriakakou (2008)	Greece	Case–control	–	7	RIA	Day 1 of life	3rd centile	Actual weight
Laivouri (2006)	USA	Case–control	PE	8	RIA	At admission for birth	10th centile	Actual weight
Lepercq (2003)	France	Case–control	PE	4	RIA	–	10th centile	Actual weight
Mise (a) (2007)	Japan	Cohort	CM	5	RIA	≤ 3 wks before birth	10th centile	Actual weight
Mise (b) (2007)	Japan	Cohort	CM	5	RIA	≤ 3 wks before birth	10th centile	Actual weight
Nezar (2009)	Egypt	Case–control	CM	6	ELISA	At birth	10th centile	Ultrasound
Orbak (2001)	Turkey	Case–control	–	5	RIA	At birth	10th centile	Actual weight
Savvidou (a) (2008)	UK	Cohort	PE	6	RIA	–	5th centile	Actual weight
Savvidou (b) (2008)	UK	Cohort	–	6	RIA	–	5th centile	Ultrasound
Tamura (a) (1998)	USA	Cohort	–	6	RIA	[a] < 22 wks	[b]15th centile	Actual weight
Tamura (b) (1998)	USA	Cohort	–	6	RIA	[a] < 22 wks	[b]15th centile	Actual weight
Tamura (c) (1998)	USA	Cohort	–	6	RIA	[a] < 22 wks	[b]15th centile	Actual weight
Tamura (d) (1998)	USA	Cohort	–	6	RIA	[a]22–27 wks	[b]15th centile	Actual weight
Tamura (e) (1998)	USA	Cohort	–	6	RIA	[a]22–27 wks	[b]15th centile	Actual weight
Tamura (f) (1998)	USA	Cohort	–	6	RIA	[a]22–27 wks	[b]15th centile	Actual weight
Tamura (g) (1998)	USA	Cohort	–	6	RIA	[a]28–33 wks	[b]15th centile	Actual weight
Tamura (h) (1998)	USA	Cohort	–	6	RIA	[a]28–33 wks	[b]15th centile	Actual weight
Tamura (i) (1998)	USA	Cohort	–	6	RIA	[a]28–33 wks	[b]15th centile	Actual weight
Tamura (j) (1998)	USA	Cohort	–	6	RIA	[a]34–39 wks	[b]15th centile	Actual weight
Tamura (k) (1998)	USA	Cohort	–	6	RIA	[a]34–39 wks	[b]15th centile	Actual weight
Tamura (l) (1998)	USA	Cohort	–	6	RIA	34–39 wks	[b]15th centile	Actual weight
Yildiz (2002)	Turkey	Case–control	PE; CM	5	RIA	At birth	10th centile	Ultrasound
Zareaan (2002)	Iran	Case–control	CM	6	ELISA	At admission for birth	10th centile	Ultrasound

CM, congenital malformations; *ELISA*, enzyme-linked immunosorbent assay; *IRMA*, immunoradiometric assay; *NOS*, Newcastle–Ottawa Scale; *PE*, preeclampsia; *RIA*, radioimmunoassay; *SD*, standard deviation; *SGA*, small for gestational age; *wks*, weeks

[a] Studies performed by Tamura et al. were divided into (a) leptin concentration measured at < 22 weeks and maternal BMI < 19.8, 19.8–28.9, and ≥ 29.0; (b) leptin concentration measured at 22–27 weeks and maternal BMI < 19.8, 19.8–28.9, and ≥ 29.0; (c) leptin concentration measured at 28–33 weeks and maternal BMI < 19.8, 19.8–28.9, and ≥ 29.0, and 28.9, and ≥ 29.0; and (d) leptin concentration measured at 34–39 weeks and maternal BMI < 19.8, 19.8–28.9, and ≥ 29.0, respectively

[b] The 15th centile birthweight in Alabama nearly corresponds to 10th centile birthweight defined by Williams et al.

(i.e., the 5th question of the NOS) in cohort studies than in case–control studies ($P = 0.006$). By adjusting for a potential cofounder, i.e., limiting to cut-off points of 3rd or 5th centile, the SMD also changed to show a significant increase in maternal blood leptin concentration in SGA neonates compared to healthy controls (Table 2) [2, 16, 26]. However, it was unclear whether this change was generalizable, because all four studies selected by limitation to cut-off points of 3rd or 5th centile were extracted from only three data sources. Indeed, two of these four studies did not set the participant criteria to exclude preeclampsia, associated with SGA neonates, at risk of increased leptin concentration in maternal blood (Table 1) [16, 26], and one study showed high blood pressure, possibly close to the threshold of preeclampsia, in mothers with SGA neonates compared to healthy controls [26]. Moreover, maternal blood leptin concentration may not be pathophysiologically increased in early-onset IUGR, more likely including birthweight below 3rd or 5th centile, by placental hyperoxia due to failure of oxygen transport from the intervillous space to the umbilical vein [13–15, 17], as described in detail in the following paragraph. Egger's test did not reveal any publication bias (Supplementary Fig. 2).

The results of the present study suggest the following etiological mechanism. The production of placental leptin that is transferred to the maternal circulation is increased by hypoxia in the placenta [13, 14]. IUGR may be associated with reduced transformation of the uteroplacental arteriole by extravillous trophoblast [14], i.e., reduced perfusion into the placenta, possibly resulting in hypoxia

Table 2 Results of meta-analysis and subgroup analysis

Category (number of studies)	SMD		I^2 (%)	Meta-regression *P* value
	Mean	95% CI		
Total population ($n = 32$)	0.116	− 0.050 to 0.282	61.8	–
Excluding PE ($n = 12$)	− 0.087	− 0.320 to 0.147	56.1	0.054
Excluding CM ($n = 9$)	0.294	− 0.135 to 0.723	79.9	0.213
Excluding PE or CM ($n = 17$)	0.063	− 0.191 to 0.317	72.9	0.485
Japan ($n = 2$)	0.674	0.218 to 1.129	0.0	0.107
Turkey ($n = 5$)	− 0.018	− 0.480 to 0.445	61.6	0.530
UK ($n = 2$)	0.404	− 0.595 to 1.403	80.0	0.394
USA ($n = 17$)	− 0.040	− 0.174 to 0.095	21.5	0.083
Asia ($n = 2$)	0.674	0.218 to 1.129	0.0	0.107
Europe ($n = 5$)	0.388	− 0.010 to 0.786	58.1	0.173
The Middle East ($n = 8$)	0.118	− 0.365 to 0.600	80.0	0.967
North America ($n = 17$)	− 0.040	− 0.174 to 0.095	21.5	0.083
Developing countries ($n = 5$)	0.293	− 0.449 to 1.034	87.1	0.461
Developed countries ($n = 27$)	0.086	− 0.069 to 0.240	47.8	–
Cohort studies ($n = 18$)	0.227	0.085 to 0.369	17.7	0.205
Case–control studies ($n = 14$)	0.002	− 0.294 to 0.298	75.7	–
Prospective data ($n = 2$)	0.012	− 0.770 to 0.794	74.9	0.595
Retrospective data ($n = 2$)	0.404	− 0.595 to 1.403	80.0	–
NOS score ≥ 7 ($n = 8$)	− 0.078	− 0.407 to 0.251	68.6	0.175
NOS score < 7 ($n = 24$)	0.187	− 0.003 to − 0.376	57.4	–
Blood sampling in 33 wks or later ($n = 13$)	0.190	− 0.130 to 0.510	71.9	0.291
Blood sampling in 32 wks or earlier ($n = 7$)	− 0.099	− 0.304 to 0.105	0.0	–
ELISA ($n = 4$)	0.327	− 0.636 to 1.289	90.3	0.452
RIA ($n = 25$)	0.067	− 0.098 to 0.233	49.1	0.342
IRMA ($n = 3$)	0.281	− 0.001 to 0.563	0.0	0.625
SGA diagnosed by actual birthweight ($n = 27$)	0.073	− 0.036 to 0.182	44.7	0.426
SGA diagnosed by ultrasound estimation ($n = 5$)	0.297	− 0.469 to 1.064	88.0	–
Cut-off point of 10th or 15th centile ($n = 28$)	0.046	− 0.119 to 0.210	56.6	0.027
Cut-off point of 3rd or 5th centile ($n = 4$)	0.628	0.152 to 1.103	54.7	–

CI, confidence interval; *CM*, congenital malformations; *ELISA*, enzyme-linked immunosorbent assay; *NOS*, Newcastle–Ottawa Scale; *PE*, preeclampsia; *SD*, standard deviation; *SGA*, small for gestational age; *SMD*, standardized mean difference; *wks*, weeks

[13–15, 17]. However, it is possible that the site of placental leptin production, the syncytiotrophoblast [17, 27], is not hypoxic in IUGR [13–15, 17]. The pathogenic conditions of some IUGR, possibly typically the early-onset form, involve reduced oxygen extraction from the intervillous space to the fetoplacental circulation, and therefore the intervillous blood to which syncytiotrophoblast cells are exposed may be chronically hyperoxic [13–15, 17]. Alternatively, these placental cells relevant to leptin production in IUGR pregnancies may not respond normally to hypoxia [13, 14]. This mechanism is likely to underlie the lack of a significant difference in maternal blood leptin concentration between SGA neonates and healthy controls.

Consequently, monitoring of leptin concentration in maternal blood may not be etiologically useful for earlier identification of mothers at risk of delivering SGA neonates to improve their mortality, morbidity, and health status in adulthood. On the other hand, a meta-analysis involving 1520 women and their neonates and at least one later study involving 510 women and their neonates suggested a significant difference in cord blood leptin between SGA neonates and healthy controls [20, 24]. Therefore, future studies are required for comparison between maternal and neonatal blood leptin concentrations in SGA neonates and healthy controls.

Strengths and limitations

This study had a number of strengths. First, there was consistency in the study procedure between the present study and the guidelines to conduct meta-analysis [8]. Second, there was internal validity, as supported by the inclusion of overall good-quality studies, and external validity, as supported by 32 studies involving 1734 women and their neonates in Asia, Europe, the Middle East, and North America [1–3, 5, 9, 12, 13, 16–19, 21, 22, 26, 30, 33, 34]. Third, there were no heterogeneity sources, confounders, or publication bias that would likely affect interpretation of the results (Table 2 and Supplementary Fig. 2).

This study also had some limitations, the first of which was that the reports were searched and reviewed by only a single person and non-English articles were excluded. Second, the results could not be extrapolated to groups that were not subjected to subgroup analysis, such as males vs. females, low birthweight, and multiple pregnancies. Third, some confounders would likely be identified in future meta-analyses including larger numbers of studies.

In conclusion, the results of the present study provided intriguing conclusions for pediatricians, obstetricians, and

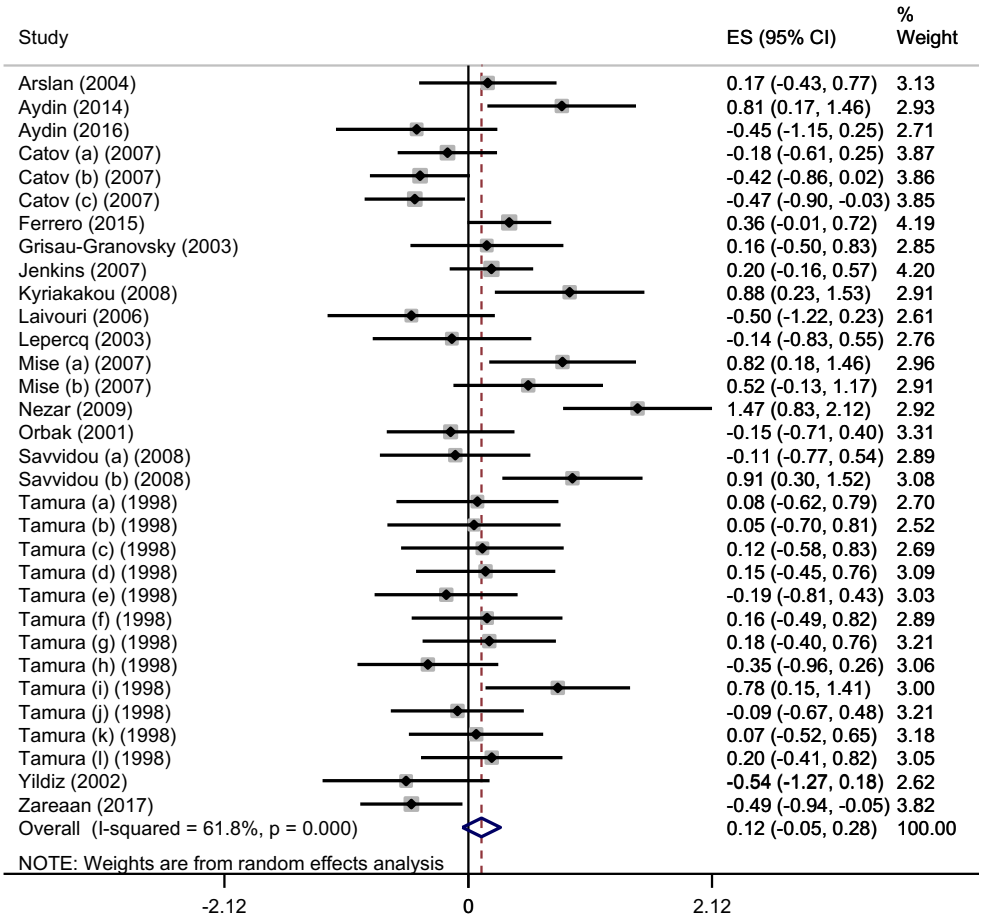

Fig. 1 Forest plot of meta-analysis. CI, confidence interval; ES, effect size. The effect size is the standardized mean difference (SMD) in maternal blood leptin concentration between small for gestational age (SGA) neonates and healthy controls. Synthetic evidence did not indicate statistical significance of SMD in maternal blood leptin concentration between SGA neonates and healthy controls ($n = 32$, $P = 0.172$)

other health practitioners who seek to identify SGA at an earlier stage to reduce the rates of neonatal mortality and morbidity as well as adulthood metabolic complications. Synthetic evidence indicated that there is no statistically significant difference in maternal blood leptin concentration between SGA neonates and healthy controls.

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Authors' Contributions EG, the corresponding author, is responsible for literature search, figures, study design, data collection, data analysis, data interpretation, and writing.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

Informed consent Not required.

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