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Original Article

Blood adiponectin concentration at birth in small for gestational age neonates: A meta-analysis

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ABSTRACT

Aims: Small for gestational age (SGA) is associated with increased rates of neonatal mortality and morbidity. Adiponectin secreted from adipose tissue is implicated in the etiology of death and illness during infancy. SGA is also a likely risk factor for the development of metabolic and clinical complications in adulthood. The present study was performed to determine whether SGA neonates and healthy controls show differences in blood adiponectin concentration at birth.

Methods: Databases were searched to identify English-language studies providing the numbers of SGA neonates, the numbers of healthy controls, and the means and standard deviations (SDs) of blood adiponectin concentrations at birth in both groups. Study quality was assessed using the Newcastle–Ottawa Scale (NOS). A meta-analysis was performed to summarize the standardized mean differences (SMDs) in blood adiponectin concentration between SGA neonates and healthy controls.

Results: The results summarized from five good quality (i.e., NOS score $\geq$ 5) studies involving 253 neonates showed that blood adiponectin concentration was significantly lower in SGA neonates than in healthy controls ($P = 0.016$), and the effect was moderate (i.e., SMD = 0.4–0.7).

Conclusions: Synthetic evidence indicated that blood adiponectin concentration at birth is lower in SGA neonates than in healthy controls.

1. Introduction

Small for gestational age (SGA) has been suggested to be associated with increased rates of neonatal mortality and morbidity [1–3]. Adiponectin is a biologically active substance secreted from adipose tissue, which is thought to have a growth-promoting effect through its insulin-sensitizing action and to play a key role in fetal growth [4,5]. A number of studies have addressed the role of adiponectin in the biochemical etiology of death and illness during infancy [6–8]. In addition, SGA is a likely risk factor for the development of metabolic and clinical complications in later life, such as obesity, high blood pressure, glucose metabolism disorders, and adipose tissue dysfunction [4].

There is evidence that cord blood adiponectin concentration is reduced in SGA neonates compared with healthy controls [9]. However, the morbidity status of neonates may be more directly reflected by adiponectin concentration in their own blood than that in the cord blood. There have been conflicting reports regarding whether the blood adiponectin concentration differs between SGA neonates and healthy controls [10–14].

Here, a meta-analysis including good-quality studies was performed to examine the differences in blood adiponectin concentration at birth between SGA neonates and healthy controls.

2. Materials and methods

2.1. Primary outcome and selection criteria

The primary outcome of this study was the standardized mean difference (SMD) [15] in blood adiponectin concentration at birth (i.e., on the 1st or 2nd day of life) between SGA neonates and healthy controls. SGA was defined as birthweight below a centile value (e.g., 3rd and 10th centile) or a value multiplied by the standard deviation (SD) (e.g., $-2 \times$ SD) for gestational age. The inclusion criteria were all English-language studies that provided the

Abbreviations: ELISA, enzyme-linked immunosorbent assay; NOS, Newcastle–Ottawa Scale; RIA, radioimmunoassay; SD, standard deviation; SGA, small for gestational age; SMD, standardized mean difference.

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numbers of SGA neonates, the means and SDs of adiponectin concentration in the SGA neonates blood at birth, the numbers of healthy controls, and the means and SDs of adiponectin concentration in the healthy controls blood at birth.

2.2. Search strategies, study selection, and data extraction

PubMed (MEDLINE) was first searched (January 6, 2018) using the following terms: adiponectin AND ("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"). There were no restrictions regarding publication date. Article titles and abstracts were scanned, and those that were determined to be unrelated to the purpose of this meta-analysis were excluded. The full texts of the remaining articles were retrieved. Articles determined to be unrelated and to not satisfy the inclusion criteria by retrieving the full texts were excluded. The remaining articles were finally eligible for inclusion in the analysis. The following strategies were used to locate additional articles, the full texts of which were 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 means and SDs of blood adiponectin concentrations at birth in SGA neonates, the numbers of healthy controls, and the means and SDs of blood adiponectin concentrations at birth in healthy controls were extracted.

2.3. Study quality assessment

Study quality assessment was performed using the Newcastle–Ottawa Scale (NOS), which was designed to evaluate selection bias, comparability bias, exposure bias, and outcome bias in cohort or case-control studies [16]. 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.

2.4. 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 according to: (a) 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; (b) study characteristics, i.e., cohort vs. case-control study, prospective vs. retrospective data collection, or NOS score $\geq$7 vs. < 7; (c) adiponectin measurement, i.e., sampling only on the 1st day of life vs. others, enzyme-linked immunosorbent assay (ELISA) vs. radioimmunoassay (RIA); or (d) a cut-off point to determine SGA, i.e., birthweight below the 10th centile vs. the 3rd centile or $-2 \times$ SD (investigation of heterogeneity sources). The SMDs of blood adiponectin concentration at birth between SGA neonates and healthy controls were estimated using Hedge's g and then summarized [17]. 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 SMD was categorized as small effect (i.e., <0.4), moderate effect (i.e., 0.4–0.7), or large effect (i.e., >0.7).

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 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) [18]. Ethical approval was not required, because this study did not use the primary data of human or animal subjects.

3. Results

3.1. Systematic review

Five articles were finally eligible for the analysis [10–14] after excluding three articles in which SGA was defined as birthweight < 2500 g or 2600 g [19–21] and one article in which blood was sampled after the 2nd day of life [22] (Table 1 and Fig. 1). Five studies involving 253 neonates were extracted from these five articles [10–14] to evaluate the difference in blood adiponectin concentration at birth between SGA neonates and healthy controls

Table 1
Characteristics of included studies.

Author	Year	Country	Design	NOS score	Adiponectin		SGA		Controls
					Kit	Time	Number	Cut-off point of birthweight	Number
Bozzola [10]	2010	Italy	Case-control	9	ELISA	2nd day	29	$-2 \times$ SD	33
Kamoda [11]	2004	Japan	Case-control	6	RIA	1st day	34	$-2 \times$ SD	28
Kyriakakou [12]	2008	Greece	Case-control	6	RIA	1st day	20	3rd centile	20
Meral [13]	2011	Turkey	Case-control	6	ELISA	1st to 4th day	20	10th centile or 2500 g	20
Saito [14]	2011	Japan	Case-control	6	ELISA	1st day	19	$-2 \times$ SD	30

ELISA, enzyme-linked immunosorbent assay; NOS, Newcastle-Ottawa Scale; RIA, radioimmunoassay; SD, standard deviation.
SGA, small for gestational age.

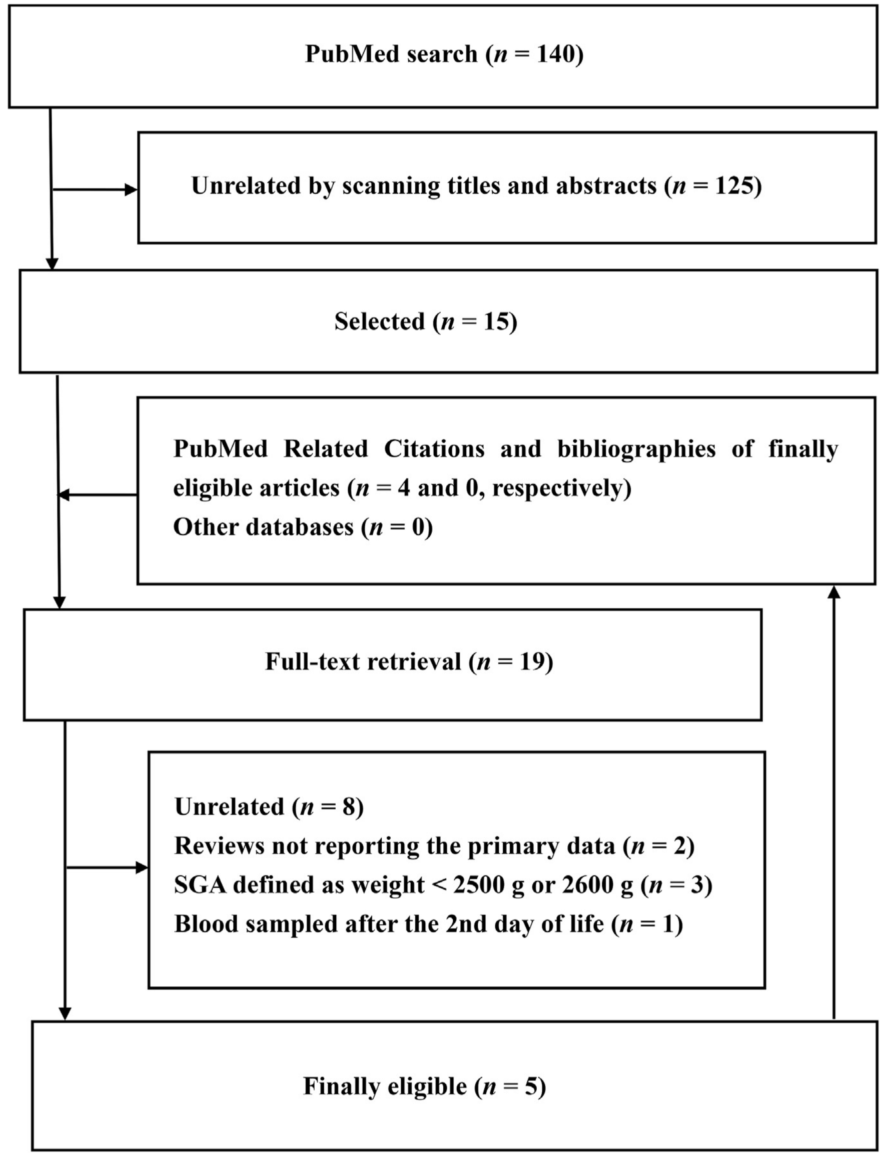

Fig. 1. Flow diagram of the meta-analysis.
Five good-quality studies involving a total of 253 neonates in Asia, Europe, and the Middle East were extracted from five finally eligible studies.

(Table 2). Studies were conducted in one developing and three developed countries in Asia, Europe, and the Middle East (Table 1). NOS scores of 6 or 9 in all of the studies suggested the inclusion of good-quality studies [10–14]. All of the included studies used case-control designs, but it was unclear whether they used prospective vs. retrospective data collection.

3.2. Meta-analysis

The SMDs of blood adiponectin between SGA and healthy controls were summarized from the heterogeneous data in the total population ($I^2 = 68.3\%$; Table 2 and Fig. 2) [10–14]. 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 developed countries [10–12,14], NOS score < 7 [11–14], sampling only on the 1st day of life [11,12,14], and a cut-off point of the 3rd centile or $-2 \times$ SD [10–12,14] ($n = 4$, 4, 3 and 4, respectively).

In the total population, blood adiponectin concentration at birth was significantly lower in SGA neonates than that in healthy controls ($n = 5$, $P = 0.016$) [10–14]. The effect was moderate (i.e., SMD = 0.4–0.7). In any subgroup, the SMD value was below zero, although not always statistically significantly (−0.711 – −0.280).

No confounder was detected, as any change from a subgroup to its counterpart had no effect on the difference in blood adiponectin concentration at birth between SGA neonates and healthy controls ($P = 0.119$–0.955; Table 2) (meta-regression analysis) [10–14]. The differences in blood adiponectin concentration at birth between SGA neonates and healthy controls did not vary after exclusion of each one of the studies from the analysis (sensitivity analysis). Based on $P < 0.1$ as the threshold of publication bias ($n = 5$) [23], no publication bias was detected in the data used to evaluate the differences in blood adiponectin concentration at birth between SGA neonates and healthy controls ($P = 0.102$) (Fig. 3).

Table 2
Results of meta-analysis and subgroup and meta-regression analysis.

Category (number of studies)	SMD			Meta-regression
	Mean	95% CI	I^2 (%)	*P* value
Total population (*n* = 5)	−0.564	−1.022 − −0.105	68.3	–
Japan (*n* = 2)	−0.505	−0.888 − −0.121	0.0	0.822
Asia (*n* = 2)	−0.505	−0.888 − −0.121	0.0	0.822
Europe (*n* = 3)	−0.280	−1.056–0.496	79.8	0.392
Developed countries (*n* = 4)	−0.376	−0.742 − −0.010	42.8	0.119
Case-control (*n* = 5)	−0.564	−1.022 − −0.105	68.3	–
NOS score <7 (*n* = 4)	−0.711	−1.008 − −0.413	43.3	0.155
Only on the 1st day of life (*n* = 3)	−0.557	−0.886 − −0.228	0.0	0.955
ELISA (*n* = 3)	−0.523	−1.340–0.293	82.8	0.807
RIA (*n* = 2)	−0.654	−1.054 − −0.254	0.0	–
SGA cut-off point of 3rd centile or −2 × SD (*n* = 4)	−0.361	−0.636 − −0.086	42.8	0.119

CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; NOS, Newcastle–Ottawa Scale; SD, standard deviation; SGA, small for gestational age; SMD, standardized mean difference.

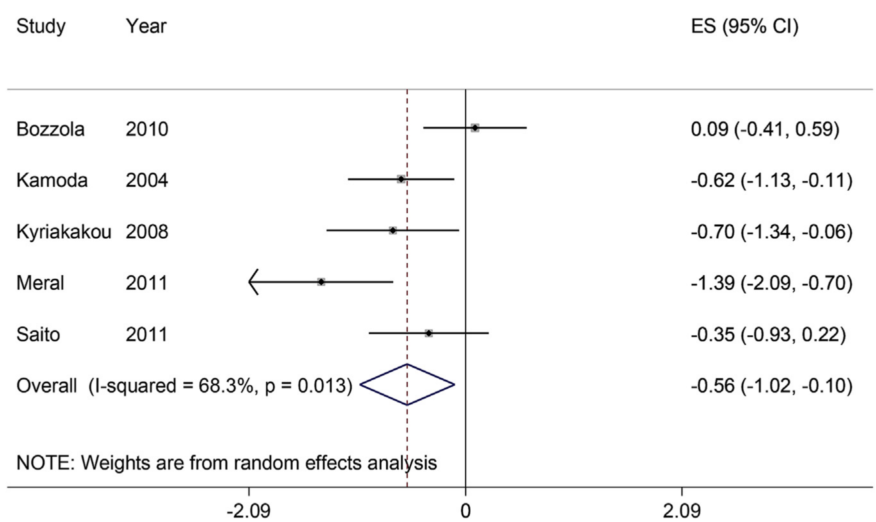

Fig. 2. Forest plot of meta-analysis.
CI: confidence interval; ES: effect size.
Effect size is the standardized mean difference (SMD) in blood adiponectin concentration at birth between small for gestational age (SGA) neonates and healthy controls. Blood adiponectin concentration at birth in SGA neonates was statistically significantly lower than that in healthy controls (*n* = 5, *P* = 0.016), and the effect was moderate (i.e., SMD = 0.4–0.7).

4. Discussion

4.1. Main findings

This is the first meta-analysis to evaluate the differences in blood adiponectin concentration at birth between SGA neonates and healthy controls. The synthetic evidence suggested that blood adiponectin concentration at birth is significantly lower in SGA neonates than in healthy controls. The findings of the present study were based on five studies involving a total of 253 neonates in five developing and developed countries in Asia, Europe, and the Middle East.[10–14] Therefore, the findings in the total population are relatively generalizable (external validity). The findings of the present study were also based on the inclusion of good-quality studies, as indicated by NOS scores of 6 or 9 (Table 1). Therefore, the findings in the total population were unlikely to have been affected by serious bias (internal validity).

4.2. Interpretations

The interpretation of the results was unlikely to be seriously affected by heterogeneity sources, confounders, or publication bias. Although homogeneity was achieved by selecting limited studies (i.e., studies limited to developed countries, NOS score < 7, sampling only on the 1st day of life, the 3rd centile or −2 × SD, etc.), the difference in blood adiponectin concentration at birth between SGA neonates and healthy controls did not change from significant to non-significant (Table 2). Meta-regression analysis did not reveal any effect of categorization on the difference in blood adiponectin concentration at birth between SGA neonates and healthy controls. Egger's test did not reveal any publication bias (Fig. 3).

The difference in blood adiponectin concentration at birth between SGA neonates and healthy controls changed from significant to non-significant by selecting studies limited to Europe or those using ELISA, which was possibly due to Type II error by reducing the number of studies included from five in the total population to three in these subgroups. In the present study, blood sampling was limited to the 1st or 2nd day of life, partly because the difference in blood adiponectin concentration between SGA neonates and healthy controls may have been influenced by possible differences in feeding between the two groups of infants. The differences in means of adiponectin concentration were transformed to the SMDs of adiponectin concentration, partly because ELISA and RIA may disagree on the value of blood adiponectin concentration [25]. The

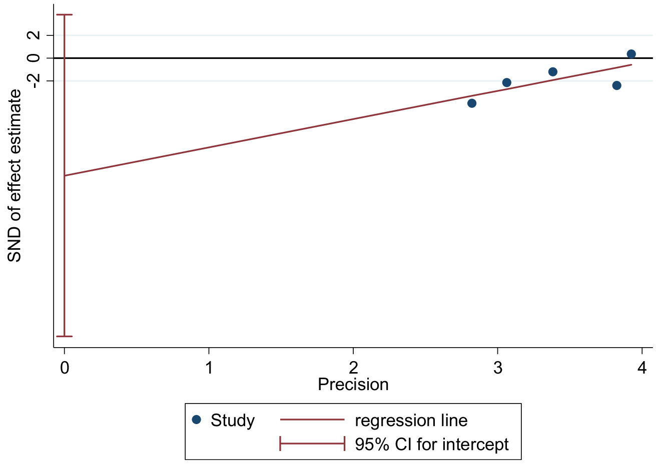

Fig. 3. Egger's regression asymmetry plot (publication bias assessment).
CI: confidence interval; SND: standard normal deviate.
"Let (t_i, v_i), $i = 1, \ldots, k$, be the estimated effect sizes and sample variances from k studies. Define the standardized effect size as $t^*_i = t_i/v_i^{1/2}$, the precision as $s^{-1} = 1/v_i^{1/2}$, and the weight as $w_i = 1/v_i$. Egger designates t^* as a *standard normal deviate* [19]. Fit t^* to s^{-1} using standard weighted linear regression with weights w and linear equation: $t^* = a + bs^{-1}$. A significant deviation from zero of the estimated intercept, $\hat{a}$, is interpreted as providing evidence of asymmetry in the funnel plot and evidence of publication bias." [24] No publication bias was detected in the data used to evaluate the difference in blood adiponectin concentration at birth between SGA infants and healthy controls, because zero was within the 95% confidence interval for intercept of the regression line.

one-score gaps of the NOS in studies by Kyriakakou et al. and Meral et al. [12,13] between the present study and a previous report [9] (Table 1) may have reflected that intra-rater reliability in NOS assessment is not guaranteed [16].

4.3. Strengths and limitations

This study had a number of strengths. First, there was overall consistency in study procedure between the present study and the guidelines to conduct meta-analysis [26]. Second, there was internal validity, as supported by the inclusion of good-quality studies, and external validity, as supported by five studies involving a total of 253 neonates in Asia, Europe, and the Middle East [10–14]. Third, there were no confounders and no publication bias that would likely affect interpretation of the results (Table 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 more studies.

5. Conclusions

In conclusion, the results of the present study provided insights into the pathogenetic etiology of high neonatal mortality and morbidity and adulthood metabolic complications both of which are observed in SGA. Synthetic evidence indicated that blood adiponectin concentration at birth is low in SGA neonates compared with healthy controls.

Author contributions

The author has accepted responsibility for the entire content of this submitted manuscript and approved submission.

Declaration of competing interests

Nothing to declare.

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