Systematic Review

Effect of Consanguinity on Low Birth Weight: A Meta-Analysis

Jalal Poorolajal MD PhD[1,2], Pegah Ameri MSc•[2], Alireza Soltanian PhD[1,3], Masoud Bahrami MSc[2]

Abstract

Background: Consanguinity (when couples share at least one common ancestor) is a public health issue with a variety of distributions and incidence rates worldwide. Several epidemiological studies have explored the association between consanguinity and low birth weight (LBW). However, the results are inconsistent. This meta-analysis aimed to explore the overall association between consanguineous marriage and LBW.

Methods: We searched PubMed, Web of Science, Scopus, ScienceDirect, and reference lists of articles up to May 2015. We included cohort, case-control, and cross-sectional studies addressing the association between consanguinity and LBW. We assessed heterogeneity using Q-test and I^2 statistic. We explored publication bias using the Egger's and Begg's tests and the funnel plot. We meta-analyzed the data and reported the overall odds ratio (OR) and mean difference with 95% confidence intervals (CI) using the random-effects model.

Results: We included 24 out of 3941 retrieved studies, with 44,131 participants. We indicated that LBW was associated significantly with first-cousin marriages (OR = 1.36; 95% CI: 1.03, 1.69) and non-significantly with second-cousin marriages (OR = 1.20; 95% CI: 0.49, 1.91). Furthermore, first-cousin marriages can reduce the birth weight of siblings of consanguineous couples 144 g more compared to non-consanguineous marriages.

Conclusions: This meta-analysis measured the association between consanguinity and LBW. Based on the current evidence, consanguineous marriage can increase the risk for LBW. However, further evidence based on large cohort studies conducted in different settings is required to make a robust conclusion regarding the effect of consanguinity on LBW.

Keywords: Consanguinity, low birth weight, meta-analysis

Cite this article as: Poorolajal J, Ameri P, Soltanian A, Bahrami M. Effect of consanguinity on low birth weight: A meta-analysis. *Arch Iran Med.* 2017**; 20(3):** 178 – 184.

Introduction

Consanguinity is a term used to describe the relationship between couples who are related by blood and share at least one common ancestor. Consanguineous marriage is a public health issue with a variety of distributions and incidence rates worldwide.[1,2] For clinical purposes, consanguinity is usually defined as the union between two people who are related as first or second cousins. The marriage between first-cousins (third-degree relatives) is the most common form of consanguinity worldwide.[3] The frequency of consanguinity varies across the world. Although the frequency of marriage with relatives is very low in the Western world, consanguinity is relatively common in the Eastern world, particularly in the Middle East, where, in some countries, they account for over half of all marriages.[1,4]

Epidemiological studies have shown that consanguinity is associated with several adverse health outcomes, because it favors the reemergence of harmful recessive alleles that run in families and hence, increases the prevalence of rare genetic congenital anomalies.[5,6] There is strong evidence showing that the offspring of consanguineous unions may be at increased risk for perinatal and postnatal mortality and morbidity, stillbirth, preterm labor, childhood death, and intellectual disability.[2,6–9]

Low birth weight (LBW) is associated with several short- and long-term consequences and continues to be a major global public health problem, representing more than 20 million births a year.[10] LBW is subject to several risk factors and is responsible for fetal and neonatal mortality and morbidity, poor cognitive development and many chronic diseases later in life.[11–14] Several epidemiological studies have explored the association between consanguinity and LBW. However, the results are inconsistent. Some studies have reported a direct association between the two,[15–18] while others have reported an inverse association.[19–21] To date, no meta-analysis has been conducted to explore the relationship between consanguineous marriage and LBW. This meta-analysis aimed to estimate the overall association between consanguinity and LBW.

Materials and Methods

Criteria for including studies

Cohort, case-control, and cross-sectional studies addressing the association between consanguineous marriage and LBW were included irrespective of language, nationality, race, and religion. The observational studies reporting the rate of LBW among consanguineous marriages without a comparison group were excluded.

Authors' affiliations: [1]Modeling of Non-communicable Diseases Research Center, Hamadan University of Medical Sciences, Hamadan, Iran, [2]Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran, [3]Department of Biostatistics, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran.

•Corresponding author and reprints: Pegah Ameri MSc, Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Shahid Fahmideh Ave. Postal Code: 6517838695, Hamadan, Iran. Tel: +98-81-38380090, Fax: +98-81-38380509, E-mail: pegah.ammeri@gmail.com.

Accepted for publication: 25 January 2017

The exposure of interest was consanguineous marriage, which was defined as marriage between a man and a woman who are related by blood and share at least one common ancestor, including first or second cousins.[3] The primary outcome of interest was LBW which was defined as weight at birth less than 2500 g.[10]

Search methods

The search strategy was as follows: (consanguinity or consanguineous or blood relation or cognation) and (birth weight or LBW or underweight)

The main bibliographic databases, including PubMed, Web of Science, Scopus, and ScienceDirect were searched up to May 2015. The reference lists of all included studies were scanned and the corresponding authors were contacted for additional eligible studies.

Data collection and analysis

Two authors (PA and MB) independently screened the titles and abstracts of the retrieved studies and decided which studies met the inclusion criteria of this meta-analysis. Disagreements between the two authors were arbitrated by a senior author (JP).

An electronic data sheet was developed and used for data extraction. Two authors (PA and MB) extracted data independently. Disagreements between the two authors were arbitrated by a senior author (JP). The following data were collected: first author's name, year of publication, country, age mean/range, gender of neonate, type of consanguinity (first-cousins, second-cousins, both), study design (cohort, case-control, cross-sectional), sample size, odds ratio with associated 95% confidence interval (CI), and mean birth weight and associated standard deviation (SD).

The quality of reporting of the included studies was explored using Newcastle Ottawa Statement (NOS) Manual.[22] The NOS scale has been developed to assess the quality of non-randomized studies in terms of design and content. This scale consists of a set of items, allocating a maximum of nine stars to the following domains: selection, comparability, exposure, and outcome. In this review, studies with seven star-items or more were considered high-quality and those with six star-items or less were considered low-quality.

Heterogeneity was explored using Q-test[23] and its quantity was measured using the I^2 statistic.[24] Publication bias was assessed using the Egger's[25] and Begg's[26] tests and visualized by the funnel plot.

The effect of consanguinity on LBW was expressed using odds ratio (OR) and mean difference (MD) with associated 95% confidence interval (CI). OR is the relative odds of outcome in the exposed group (consanguinity) versus the non-exposed group (non-consanguinity) occurring at any given point in time. Wherever reported, we used full adjusted forms of OR rather than crude OR.

Since included studies came from different settings, genetic background, and socioeconomic status, data were analyzed and the results were reported using a random effects model.[27] All statistical analyses were performed at a significance level of 0.05 using Stata software, version 11 (StataCorp, College Station, TX, USA).

Sensitivity analysis

We used sequential algorithm[28] to achieve the minimum final I^2 the desired 50% threshold. In this approach, for this meta-analysis of 24 studies, we performed 24 new meta-analyses, where one study was excluded from the calculations each time. The study that was responsible for the largest decrease in I^2 was dropped and a new set of 24−1 studies was created. When two or more studies caused exactly the same decrease in I^2 by their exclusion, we dropped the study with the largest decrease in Q. We continued this process until I^2 decreased below the desired pre-set threshold. In the last step, if there was a chance more than one omitted studies could result in I^2 dropping below the desired threshold, we reported the minimum I^2.

Results

Description of studies

We retrieved 3941 references up to May 2015, including 3414 references through searching electronic databases, and 527 references through checking other sources, including reference lists or personal contact with authors of the included studies. We excluded 1057 duplicates and 2774 clearly irrelevant references through reading titles and abstracts. Of the 110 references considered potentially eligible after screening, 86 studies were excluded because they did not meet the inclusion criteria, because they assessed the relationship between LBW and consanguinity along with other risk factors such as eclampsia and preeclampsia, socioeconomic status, or assessed the association between consanguinity and baby growth or perinatal events rather than birth weight. Eventually, 24 studies were included in the meta-analysis, consisting of 5 cohort studies,[16,17,21,29,30] 2 case-control studies[18,19] and 17 cross-sectional studies[2,15,20,31–44] (Figure 1). All included studies were published in English. In cases of multiple publication, the last report was used.

The characteristics of the included studies are summarized and listed in Table 1. The included studies involved 44,131 participants. Twelve studies reported the association between consanguineous marriage and LBW using OR and twelve studies reported mean difference. The quality of reporting and the risk of bias of the included studies were explored using NOS. Based on this scale, four studies had high quality and the remainder had low quality.

Effect of exposure

The effect of consanguinity on LBW is shown in Figures 2. Based on this forest plot, LBW was significantly associated with first-cousin marriages (OR=1.36; 95% CI: 1.03, 1.69) and non-significantly with second-cousin marriages (OR = 1.20; 95% CI: 0.49, 1.91). However, overall, consanguinity can increase the risk of LBW (OR = 1.26; 95% CI: 1.04, 1.49). The odds ratios reported here are on the basis of random effects model. That means, the odds ratios reported here denote the average effect. The true effect of consanguinity on LBW may vary from study to study, because of the diversity in the study populations in term of genetics, lifestyle, socioeconomic status, nutrition, and so on.

There was an extreme value (outlier) among the studies (not shown in the forest plot). This outlier consisted of a cohort of 4498 siblings of consanguineous marriages.[21] According to the results of this study, the proportion of LBW was much lower in consanguineous marriages compared to non-consanguineous marriages (20.0% versus 57.3%).

The mean difference of birth weight between consanguineous and non-consanguineous marriages is given in Figure 3. According to the results, first-cousin marriages can reduce birth weight

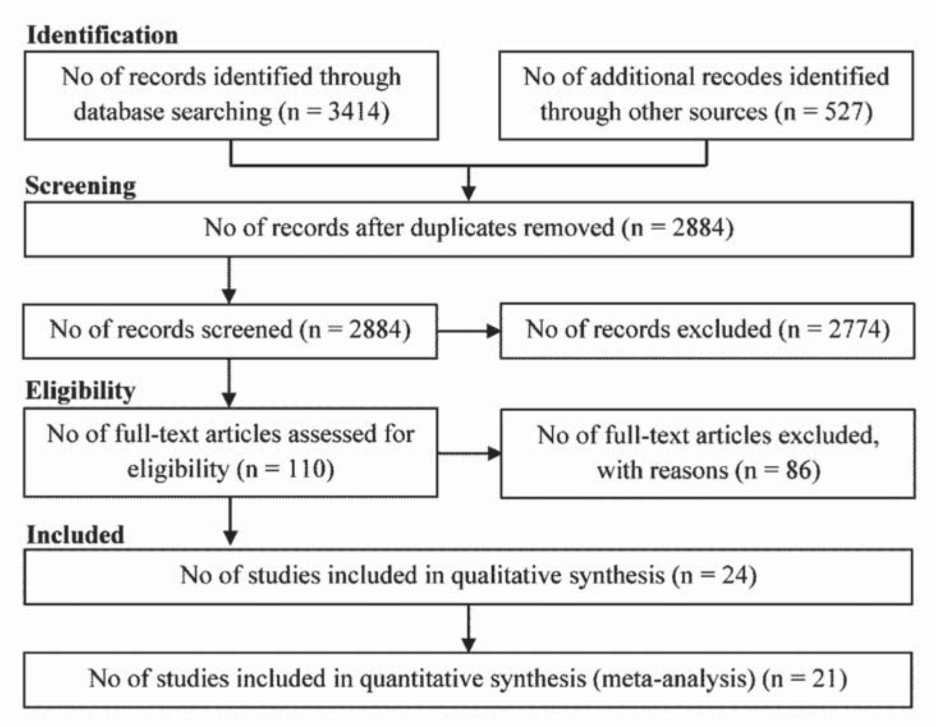

Figure 1. Flow of information through the different phases of the systematic review

Table 1. Summary of studies results

1st author, year	Country	Age	Consanguinity*	Study	Estimate	Sample	Quality
Badshah, et al. (2008)	Pakistan	26.65	Overall	Cross-sectional	Odds ratio	1,039	Low
Bellad, et al. (2012)	India	22.55	Overall	Cohort	Odds ratio	601	High
Bener, et al. (2013)	Qatar	29.59	1st, 2nd, Overall	Case-Control	Odds ratio	1,726	Low
Bener, et al. (2012)	Qatar	30.46	Overall	Cohort	Odds ratio	1,674	Low
Bromiker, et al. (2004)	Israel	18.50	Overall	Cohort	Odds ratio	540	High
Dawodu, et al. (1996)	UAE	26.18	1st, 2nd, Overall	Case-Control	Odds ratio	1,172	Low
Joseph, et al. (2014)	India	38.80	Overall	Cross-sectional	Odds ratio	187	Low
Obeidat, et al. (2010	Jordan	27.20	Overall	Cross-sectional	Odds ratio	2,693	Low
Saedi-Wong, et al. (1989)	Saudi Arabia	No data	1st, Overall	Cross-sectional	Odds ratio	4,497	Low
Wong, et al. (1990)	Saudi Arabia	18–24	1st, Overall	Cohort	Odds ratio	4,498	Low
Al-Eissa, et al. (1991)	Saudi Arabia	27.27	1st, 2nd, Overall	Cohort	Odds ratio	1,056	High
Zakar, et al. (2015)	Pakistan	27.07	1st, Overall	Cross-sectional	Odds ratio	5,724	Low
Basaran, et al. (1994)	Turkey	No data	1st, Overall	Cross-sectional	Mean	2,880	Low
Honeyman, et al. (1987)	Pakistan	No data	1st, Overall	Cross-sectional	Mean	260	Low
Jaber, et al. (1997)	Israel	No data	1st, Overall	Cross-sectional	Mean	1,219	Low
Khlat, et al. (1989)	Lebanon	No data	Overall	Cross-sectional	Mean	936	Low
Magnus, et al. (1985)	Norway	No data	1st, Overall	Cross-sectional	Mean	4,795	Low
Paddaiah, et al. (1980)	India	No data	Overall	Cross-sectional	Mean	4,826	Low
Paddaiah, et al. (2001)	India	No data	Overall	Cross-sectional	Mean	1,445	Low
Ramankutty, et al. (1983)	Iraqi	26.36	Overall	Cross-sectional	Mean	1,170	High
Saiful-Islam, et al. (2009)	Bangladesh	No data	Overall	Cross-sectional	Mean	150	Low
Shami, et al. (1991)	Pakistan	23.10	1st	Cross-sectional	Mean	613	Low
Sibert, et al. (1979)	India	No data	1st, Overall	Cross-sectional	Mean	322	Low
Slatis, et al. (1961)	United States	No data	Overall	Cross-sectional	Mean	108	Low

*1st cousins; 2nd cousins; Overall (both 1st and 2nd cousins)

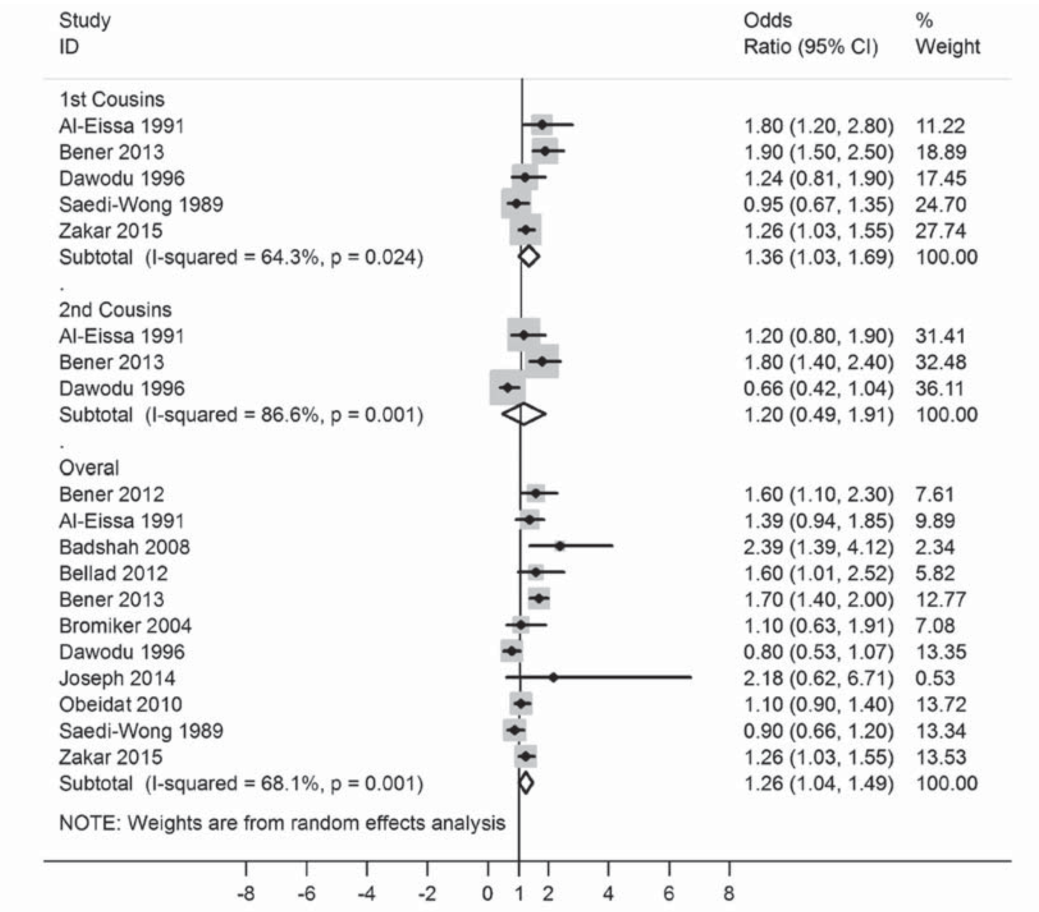

Figure 2. Forest plot of the association between consanguinity and low birth weight using odds ratio

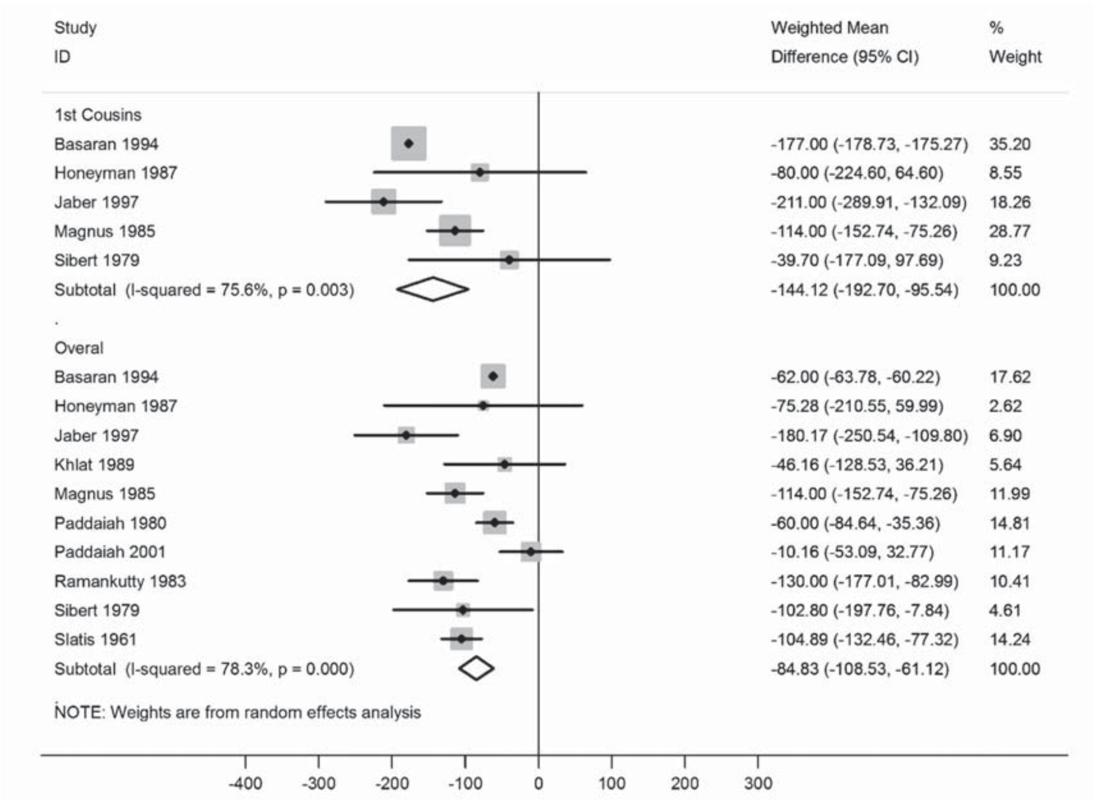

Figure 3. Forest plot of the association between consanguinity and low birth weight using mean difference

more than 144 g compared to non-consanguineous marriages, on average. However, the mount of birth weight reduction may vary across different populations.

There were two extreme values (outliers) among the studies (not shown in the forest plot). The first outlier[40] was a cross-sectional study consisting of 150 infants. This study indicated that consanguineous marriages can reduce birth weight by 1060 g. The second outlier[41] was a cross-sectional study consisting of 613 infants. This study reported that consanguinity can reduce birth weight by 504 g.

Heterogeneity and publication bias

The presence of heterogeneity was explored using Q-test and the quantity of heterogeneity was measured using the I^2 statistic (Figure 2). The results showed moderate heterogeneity (I^2 = 64.3%, *P* = 0.024) among studies addressing the association between first-cousin marriages and LBW and severe heterogeneity (I^2 = 86.6%, *P* = 0.001) among studies addressing the association between second-cousin marriages and LBW. The results of the heterogeneity test were also significant for the overall association between heterogeneous marriage and LBW (I^2 = 68.1%, *P* = 0.001).

We explored the possibility of publication bias using Begg's and Egger's statistical tests and visualized by the funnel plot (Figure 4). The results of Begg's and Egger's tests indicated no evidence of publication bias among the studies reflecting the association between consanguinity and LBW (*P* = 0.194 and *P* = 0.240, respectively). The funnel plot confirmed these findings. Figure 4 shows that studies are scattered nearly symmetrically on both sides of the horizontal line reflecting no evidence of publication bias among the included studies.

Subgroup analysis

We performed subgroup analysis based on study type and the quality of the included studies. Only one cohort study[30] separately reported the association between LBW and first-cousin marriages (OR = 1.80; 95% CI: 1.20, 2.80) and second-cousin marriages (OR = 1.20; 95% CI: 0.65, 1.75). Based on case-control studies, the association between LBW and first-cousin marriages was 1.58 (95% CI: 0.93, 2.23) and second-cousin marriages was 1.21 (95% CI: 0.10, 2.33). According to the cross-sectional studies, the association between LBW and first-cousin marriages was 1.13 (95% CI: 0.82, 1.43). No cross-sectional study reported the association between LBW and second-cousin marriages.

Since the number of high-quality studies was limited, subgroup analysis based on high-quality studies was performed only for first-cousin marriages (OR = 1.69; 95% CI: 1.02, 1.69). According to the low-quality studies, the association between LBW and first-cousin marriages was 1.31 (95% CI: 0.96, 1.65), and that of second-cousin marriages was 1.21 (95% CI: 0.10, 2.33).

Sensitivity analysis

There was evidence of moderate to high heterogeneity among studies addressing the association between LBW and consanguinity; thus, we performed sensitivity analysis based on the sequential algorithm to achieve between-study homogeneity. We achieved the minimum desired I^2 threshold (50%) by omitting two studies[17,21] from the meta-analysis addressing the association between LBW and first-cousin marriages (OR = 1.20; 95% CI: 0.95, 1.46; I^2 = 32.7%) and the overall association between LBW and consanguinity (OR = 1.17; 95% CI: 0.97, 1.36; I^2 = 50.3%).

Discussion

We assessed the association between consanguinity and LBW not only by summarizing the odds ratio estimates reported by the epidemiological studies, but also by summarizing the mean difference of birth weight. Both methods indicated that consanguineous marriage can increase the risk of LBW. The severity of LBW was greater in the offspring of first-cousin

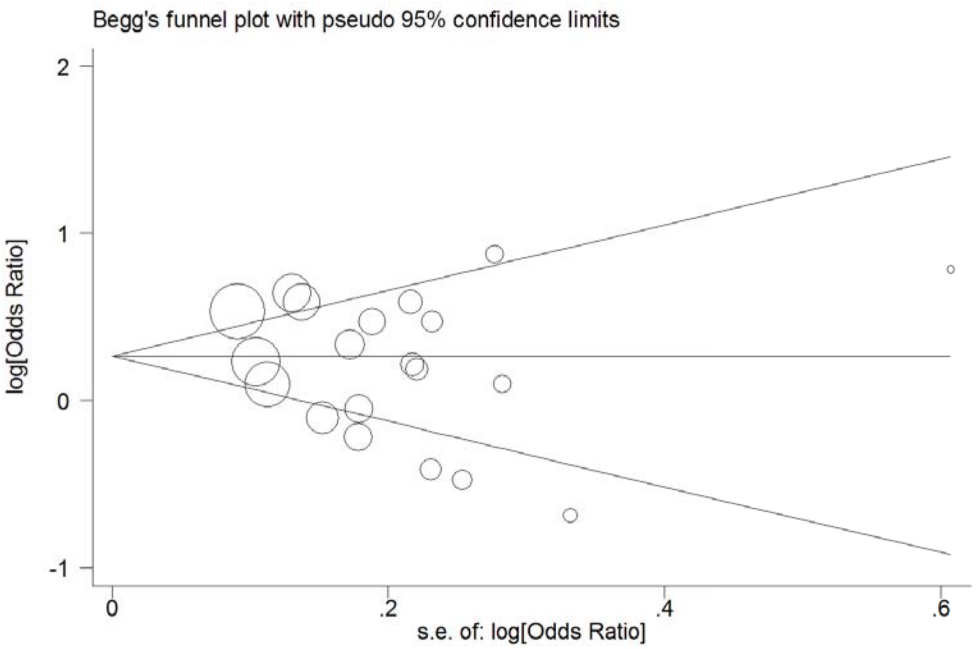

Figure 4. Funnel plot of included studies addressing the association between consanguinity and low birth weight

marriages than those of second-cousin marriages. Indeed, there is an apparent exposure-response relationship between consanguinity and LBW. As the blood relation between parents become closer, the risk of LBW also increases. When, an exposure-response relationship is present, it is strong evidence for a causal relationship.[45]

Marriage between close relatives is discouraged or may even be illegal in many countries such as North America, while, in some countries, particularly in the Middle East, Asia, and Africa, the people prefer to marry with relatives.[46] It is estimated that 20% to 60% of all marriages in some cultures are between close biological relatives.[47]

The statistical tests inspecting heterogeneity (Q-test and I^2 statistic) indicated evidence of heterogeneity between included studies. However, these statistical tests should be interpreted with caution. When the sample size of the studies is small or the number of studies is limited, the Q-test has low statistical power. On the other hand, when the sample size or the number of the included studies is large, the test has high power in detecting a small amount of heterogeneity that may be clinically unimportant.[23] Therefore, a part of observed heterogeneity can be attributed to the number of studies (21 studies) included in the meta-analysis and the large sample size (involving 44,131 participants). However, another part of observed heterogeneity can be attributed to the variation in population sizes, sociodemographic characteristics, study design, and potential confounding factors.

The results of the study conducted by Wong, et al.[21] were inconsistent with the results of other studies included in the meta-analysis. According to the results of that study, the probability of LBW among siblings of consanguineous marriages was reported much lower than that of non-consanguineous marriages. This estimate was made based on a limited number of participants (43 non-consanguineous marriages versus 15 consanguineous marriages). The main reason to explain this inconsistency may be the small sample size and hence possibility of random error. Another study conducted by Saiful Islam, et al.[40] was considered an outlier because the mean difference of birth weight reported by this study was much higher than the results reported by similar studies. They randomly selected 150 clinical patients (40 consanguineous and 110 non-consanguineous cases) referred to 10 hospitals and clinics due to birth-related abnormalities. The possibility of random error due to small sample size and the congenital abnormality of the patients may explain why the results of this study overestimated the mean difference of birth weight among siblings of consanguineous and non-consanguineous couples. Another study, which was considered an outlier, was conducted by Shami, et al.[41] on 613 singleton live births within 24 hours of birth. The sample size was large enough; hence, the possibility of random error was low. The sample was selected from pregnant women who referred to the local hospital for normal delivery. Therefore, no special reason was found to explain why the result of this study was different from those of similar studies. However, sociodemographic characteristics and potential unknown confounding factors may be the reason.

The variability in study design, small sample sizes, poor quality, and not controlling potential confounding factors were the main limitations and potential biases of the studies included in this met-analysis. Furthermore, we found five studies, which seemed potentially eligible to be included in the meta-analysis. However, we excluded them because we did not have access to their full text. This may raise the possibility of selection bias. Despite the above limitations, this meta-analysis could efficiently estimate the effect of consanguineous marriage on LBW using both the odds ratio estimates and the mean difference of the birth weights. We screened 3941 retrieved references and included 24 eligible studies in the meta-analysis involving 44,131 participants; however, the evidence does not seem sufficient to make a robust conclusion regarding the objective of the study for estimating the association between consanguinity and LBW.

In conclusion, this meta-analysis measured the association between consanguinity and LBW. Based on current evidence, consanguineous marriage can increase the risk for LBW. However, further large cohort studies are required to be conducted in different settings to make a robust conclusion regarding the effect of consanguinity on LBW.

Acknowledgments

This was part of a MSc thesis in epidemiology. We would like to appreciate the Vice-chancellor of Education for technical support and the Vice-chancellor of Research and Technology, Hamadan University of Medical Sciences, for financial support of this study.

Conflict of interest statement

The authors declare that they have no conflicts of interest in this work.

References

1. Hamamy H, Alwan A. Hereditary disorders in the Eastern Mediterranean Region. *Bull World Health Org.* 1994; 72(1): 145 – 154.
2. obeidat BR, Khader YS, Amarin ZO, Kassawneh M, Al Omari M. Consanguinity and adverse pregnancy outcomes: the north of Jordan experience. *Matern Child Health J.* 2010; 14(2): 283 – 289.
3. Bittles A, Speicher M, Antonarakis S, Motulsky A. *Consanguinity, genetic drift and genetic diseases in populations with reduced numbers of founders.* 4th ed. Heidelberg: Springer; 2009.
4. Bittles A. Consanguinity and its relevance to clinical genetics. *Clin Genet.* 2001;60(2):89 – 98.
5. Mumtaz G, Tamim H, Kanaan M, Khawaja M, Khogali M, Wakim G, et al. Effect of consanguinity on birth weight for gestational age in a developing country. *Am J Epidemiol.* 2007; 165(7): 742 – 752.
6. World health Organization. Congenital anomalies. Geneva: WHO; 2015 [updated April 2015; cited 4 April 2015]. 2015; Available from: URL: http://www.who.int/mediacentre/factsheets/fs370/en/, (Accessed Date: 4 April 2015).
7. Aboualsoltani F, Rahmani S, Pourbarghi M, Dolatkhah H, Aghazadeh A. The frequency of consanguineous marriages and their effects on offsprings in Tabriz city. *J Med Hum Genet.* 2009; 10(2): 198 – 207.
8. Bittles A, Black M. The impact of consanguinity on neonatal and infant health. *Early Hum Dev.* 2010; 86(11): 737 – 741.
9. Shawky R, El-Awady M, Elsayed S, Hamadan G. Consanguineous matings among Egyptian population. *Egypt J Med Human Genet.* 2011; 12(2): 157 – 163.
10. World Health Organization. *Global nutrition targets 2025 low birth weight policy brief.* Geneva: WHO/NMH/NHD/14.5; 2014.
11. Singh G, Chouhan R, Sidhu K. Maternal factors for low birth weight babies. *Med J Armed Forces India.* 2009; 65(1): 10 – 12.
12. Risnes K, Vatten L, Baker J, Jameson K, Sovio U, Kajantie E, et al. Birthweight and mortality in adulthood: a systematic review and metaanalysis. *Int J Epidemiol.* 2011; 40(3): 647 – 661.
13. Rezaeian S, Poorolajal J, Moghimbegi A, Esmailnasab N. Risk factors of congenital hypothyroidism using propensity score: A matched case-control study. *J Res Health Sci.* 2013; 13(2): 151 – 156.
14. Amirian H, Poorolajal J, Roshanaei G, Esmailnasab N. Analyzing socioeconomic related health inequality using the concentration index.

Epidemiology, Biostatistics and Public Health. 2014; 11(3): 9081 – 9086.
15. Badshah S, Mason L, McKelvie K, Payne R, Lisboa PJ. Risk factors for low birthweight in the public-hospitals at Peshawar, NWFP-Pakistan. *BMC Public Health.* 2008; 8: 197.
16. Bellad MB, Goudar SS, Edlavitch SA, Mahantshetti NS, Naik V, Hemingway-Foday JJ, et al. Consanguinity, prematurity, birth weight and pregnancy loss: a prospective cohort study at four primary health center areas of Karnataka, India. *J Perinatol.* 2012; 32(6): 431 – 437.
17. Bener A, Salameh KM, Yousafzai MT, Saleh NM. Pattern of maternal complications and low birth weight: associated risk factors among highly endogamous women. *ISRN Obstet Gynecol.* 2012; 2012: 540495.
18. Bener A, Saleh NM, Salameh KM, Basha B, Joseph S, Al Buz R. Socio-demographic and consanguinity risk factors associated with low birthweight. *J Pak Med Assoc.* 2013; 63(5): 598 – 603.
19. Dawodu A, Yousef M, Abdulrmzaq, Abdulbari B, Mani V. Biologic risk factors for low birthweight in Al Ain, United Arab Emirates. *Am J Hum Biol.* 1996; 8: 341 – 345.
20. Saedi-Wong S, Al-Frayh AR. Effects of consanguineous matings on anthropometric measurements of Saudi newborn infants. *Fam Pract.* 1989; 6(3): 217 – 220.
21. Wong SS, Anokute CC. The effect of consanguinity on pregnancy outcome in Saudi Arabia. *J R Soc Health.* 1990; 110(4): 146 – 147.
22. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2009; Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Accessed Date: 25 March 2014).
23. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration; 2008; Available from: URL: www.cochrane-handbook.org. (Accessed Date: February 2017)
24. Higgins JPT, Thompson SG, Deeks JJ, Altman D. Measuring inconsistency in meta-analyses. *BMJ.* 2003; 327: 557 – 560.
25. 2Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997; 315(7109): 629 – 634.
26. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994; 50: 1088 – 1101.
27. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986; 7: 177 – 188.
28. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *Int J Epidemiol.* 2008; 37(5): 1148 – 1157.
29. Bromiker R, Glam-Baruch M, Gofin R, Hammerman C, Amitai Y. Association of parental consanguinity with congenital malformations among Arab newborns in Jerusalem. *Clin Genet.* 2004; 66(1): 63 – 66.
30. Al-Eissa YA, Ba'Aqeel HS, Haque KN. Low birthweight in Riyadh, Saudi Arabia: Incidence and risk factors. *Ann Trop Paediatr.* 1991; 11(1): 75 – 82.
31. Basaran N, Artan S, Yazicioglu S, Sayli BS. Effects of consanguinity on anthropometric measurements of newborn-infants. *Clinical Genetics.* Apr 1994; 45(4): 208 – 211.
32. Honeyman MM, Bahl L, Marshall T, Wharton BA. Consanguinity and fetal growth in Pakistani Moslems. *Arch Dis Child.* 1987; 62(3): 231 – 235.
33. Jaber L, Merlob P, Gabriel R, Shohat M. Effects of consanguineous marriage on reproductive outcome in an Arab community in Israel. *J Med Genet.* 1997; 34(12): 1000 – 1002.
34. Joseph N, Pavan KK, Ganapathi K, Apoorva P, Sharma P, Jhamb JA. Health awareness and consequences of consanguineous marriages: A community-based study. *J Prim Care Community Health.* 2015; 6(2): 121 – 127.
35. Khlat M. Inbreeding effects on fetal growth in beirut, Lebanon. *Am J Phys Anthropol.* 1989; 80(4): 481 – 484.
36. Magnus P, Berg K, Bjerkedal T. Association of parental consanguinity with decreased birth-weight and increased rate of early death and congenital-malformations. *Clin Genet.* 1985; 28(4): 335 – 342.
37. Paddaiah G, Madhavi D. The effect of parental consanguinity and inbreeding on the anthropometric measurements of the newborn babies revisited. *IJHG.* 2001; 1(3): 187 – 190.
38. Paddaiah G, Reddy GG. Effect of consanguinity on anthropometric measurements in the newborn. *Indian J Pediatr.* 1980; 47(385): 133 – 136.
39. Ramankutty P, Tikreeti RAS, Rasaam KW, Al-Thamery DM, Yacoub AA, Mahmood DA. A study on birth weight of Iraqi children. *Journal of Tropical Pediatrics.* 1983; 29(1): 5 – 10.
40. Saiful Islam M, Ahmed S. Incidences of birth abnormalities, congenital defects and their association with consanguineous marriages in Rajshahi: A case study. *J Biosci.* 2009; 17(1): 107 – 112.
41. Shami SA, Qadeer T, Schmitt LH, Bittles AH. Consanguinity, gestational period and anthropometric measurements at birth in Pakistan. *Ann Hum Biol.* 1991; 18(6): 523 – 527.
42. Sibert JR, Jadhav M, Inbaraj SG. Fetal growth and parental consanguinity. *Arch Dis Child.* 1979; 54(4): 317 – 319.
43. Slatis H, Hoene R. The Effect of Consanguinity on the Distribution of Continuously Variable-Characteristics. *Am J Hum Genet.* 1961; 13(1 Pt 1): 28 – 31.
44. Zakar R, Zakar MZ, Aqil N, Nasrullah M. Paternal factors associated with neonatal deaths and births with low weight: evidence from Pakistan Demographic and Health Survey 2006–2007. *Matern Child Health J.* 2015; 19(**7**): 1634 – 1642.
45. Gordis L. *Epidemiology.* 5th ed. Philadelphia: Saunders; 2014.
46. Bennett RL, Motulsky AG, Bittles A, Hudgins L, Uhrich S, Doyle DL, et al. Genetic counseling and screening of consanguineous couples and their offspring: recommendations of the National Society of Genetic Counselors. *J Genet Couns.* 2002; 11(97): 97 – 120.
47. Bittles AH. *Empirical estimates of the global prevalence of consanguineous marriage in contemporary societies.* Stanford University; 1998.