Acta Dermatovenerol Croat 2014;22(2):91-96 REVIEW

Birth Weight and Atopic Dermatitis: Systematic Review and Meta-analyis

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Received: August 21, 2013
Accepted: December 15, 2013

SUMMARY Several studies examined the relationship between birth weight and atopic diseases, but no consensus has yet been reached regarding the results.

The purpose of this paper was to perform a meta-analysis of the existing studies regarding the role of birth weight in the occurrence of atopic dermatitis. We carried out an extensive search in the international databases (Pubmed, Cochrane Library, and Web of Knowledge). We selected the cross-sectional, case-control, and cohort studies which analyzed the role of birth weight in the occurrence of atopic dermatitis. We performed a meta-analysis of the selected studies, and calculated the odds ratio (OR) and corresponding 95% confidence intervals (95% CI). We included 10 studies in the final meta-analysis, which comprised 110974 patients. Weight classification was in compliance with Pediatric Nutrition Surveillance System (PedNSS) Health Indicators. In the first meta-analysis, we selected patients with low weight (below 2500 g) and atopic dermatitis and compared them with those with normal weight (2500 – 4000 g) and atopic dermatitis. The analysis showed that low birth weight represents a protective factor in the occurrence of atopic dermatitis (OR = 0.68, CI: 0.63 – 0.75, $P<0.0001$). In the second meta-analysis, we compared patients with high weight (over 4000 g) and atopic dermatitis with those with normal weight and atopic dermatitis. The results indicated that increased birth weight represents a risk factor for atopic dermatitis (OR = 1.1; CI: 1.02 – 1.17; $P = 0.01$)

Thus, low birth weight represents a protective factor for the occurrence of atopic dermatitis and high birth weight represents a risk factor for the occurrence of this disease.

KEY WORDS: dermatitis, atopic; eczema, atopic; eczema, infantile; birth weight; infant, low birth weight

INTRODUCTION

Atopic dermatitis is an inflammatory chronic skin disease and represents one of the first manifestations of "allergic march" (1). Various studies have suggested a strong relationship between the nutritional status in pregnancy, fetal growth, and diseases that appear throughout life (2,3). Anthropometric parameters at

birth reflect fetal growth as well as intrauterine and nutritional status. Several studies have examined the relationship between these measures and atopic diseases (4,5). Birth weight has been assessed in many studies, but no consensus has yet been reached.

The purpose of this work is to analyze the evidence pertaining to the relationship between birth weight and the occurrence of atopic dermatitis by carrying out a meta-analysis of studies found in international data bases. The studied population was consisted of children. The evaluated intervention was low respective high birth weight compared with normal weight. The outcome was atopic dermatitis development in children.

MATERIAL AND METHODS

Protocol registration

This review is reported according to the guidelines of the PRISMA statement. It was registered in the international prospective register of systematic reviews and received the following registration number – CRD42013004254. The protocol is publicly available at the PROSPERO website (*http://www.crd.york.ac.uk/PROSPERO*).

Description of the search protocol

During the period of November 2011 – November 2012 we carried out a detailed search in the following

Table 1. Characteristics of studies included in this meta-analysis (publishing data, the country where the study has been carried out, design, outcome measurement, diagnosis modality, follow-up time), patient characteristics (number of patients), study quality

Study	Study name	Country	Design	No of participants	Outcome	Outcome measurement	Diagnostic methods and criteria	Time from birth	Quality
Butland BK BMJ 1997	Cohort 1958	England, Wales, Scotland	prospective birth cohort studies	11195	AD	Birth register	Parents	16 years	C
Butland BK BMJ 1997	Cohort 1970	England, Wales, Scotland	prospective birth cohort studies	9387	AD	Birth register	Parents	16 years	C
Buhrer C Lancet 1999		Germany	follow-up cohort of VLBW	786	AD	Birth register	Doctor	12 months	C
Xu B Allergy 1999	1985-1986	Finland	historical follow - up from birth register	8088	AD	Questionnaires at 7 years	Parents	7 years	C
Steffensen FH Epidemiology 2000		Denmark	long - term follow-up	4795	AD	Questionnaires at 18 years	Participants	18 years	C
Hikino S Acta Pediatr 2001		Japan	follow-up cohort	21766	AD	Parent questionnaires	Parents and doctor	18 months	C
Hikino S Acta Pediatr 2001		Japan	follow-up cohort	4378	AD	Parent questionnaires	Parents and doctor	3 years	C
Kerkhof M Clin Exp Allergy 2003	PIAMA	Netherlands	follow-up birth cohort study	304	AD	Parent questionnaires	Doctor	12 monhts	C
Katz KA Clin Exp Allergy 2003		England	follow-up	10809	AD	Parent questionnaires	Parents	16 years	C
Laerum BN Clin Exp Allergy 2005	ECRHS sub-study	Norway, Denmark, Sweden, Iceland, Estonia	prospective cohort study	1683	AD	Interview	Participants		C
Linneberg A J Allergy Clin Immunol 2006		Denmark	Mother from DNBC followed prospectively	34768	AD	Parent questionnaires	Doctor	16 and 18 months	C
Lundholm C Clin Exp Allergy 2010		Sweden	follow-up twins	10132	AD	Interview	Parents	9 and 12 years	C

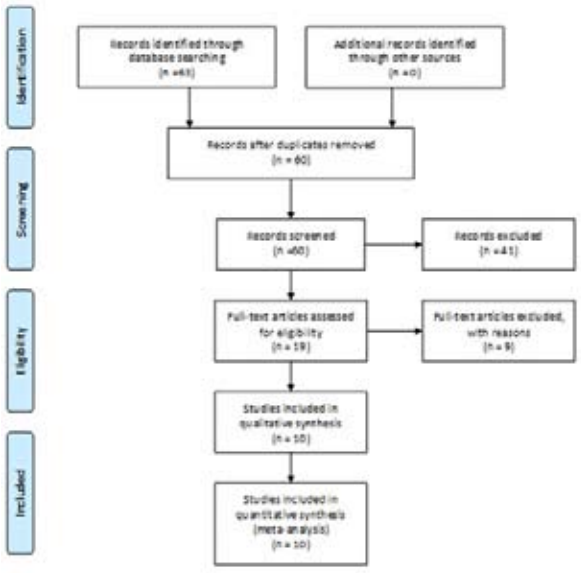

Figure 1. Flow diagram of study selection.

international data bases: Medline, Cochrane Library, and Web of Knowledge. The search retrieved the studies which analyze the risk factors for atopic dermatitis, and among these we selected the articles in which the association between birth weight and occurrence of atopic dermatitis is analyzed. The search terms were: "birth weight", "risk factors", or "birth size", and "atopic dermatitis" or "atopy".

We selected cross-sectional, case-control, and cohort studies written in English and included only the studies which contained data related to the number of patients with low birth weight (below 2500 g), with normal weight (2500 – 4000 g) and high weight (over 4000 g). The weight classification was made in accordance with PedNSS Health Indicators.

Two independent reviewers (MP and CMS) analyzed the titles and the abstracts of the studies initially identified, in order to find the studies that satisfy the selection criteria. The reference list of the selected studies was searched for other possible articles. Case reports, abstracts, systematic reviews, meta-analyses, and letters or conference presentations were excluded.

Data extraction

We determined the data we were interested in before implementing the search strategy. The data collected included the characteristics of the study (publishing data, the country where the study was carried out, design, outcome measurement, diagnosis modality, and follow-up time) as well as patient characteristics (number of patients and their weight) (Table 1).

We assessed the differences between low or high birth weight and atopic dermatitis. For each study, in the first meta-analysis we compared the patients with and without atopic dermatitis with low birth weight with patients with and without atopic dermatitis with normal birth weight; in the second meta-analysis we compared patients with and without atopic dermatitis with high birth weight with patients with and without atopic dermatitis and normal birth weight.

Statistical analysis

We evaluated the risk of atopic dermatitis occurrence in children with low or high birth weight compared with children of normal weight.

In order to calculate the size of the effect, the "random-effects" model was used, assuming the heterogeneity of studies. For the selected studies, we

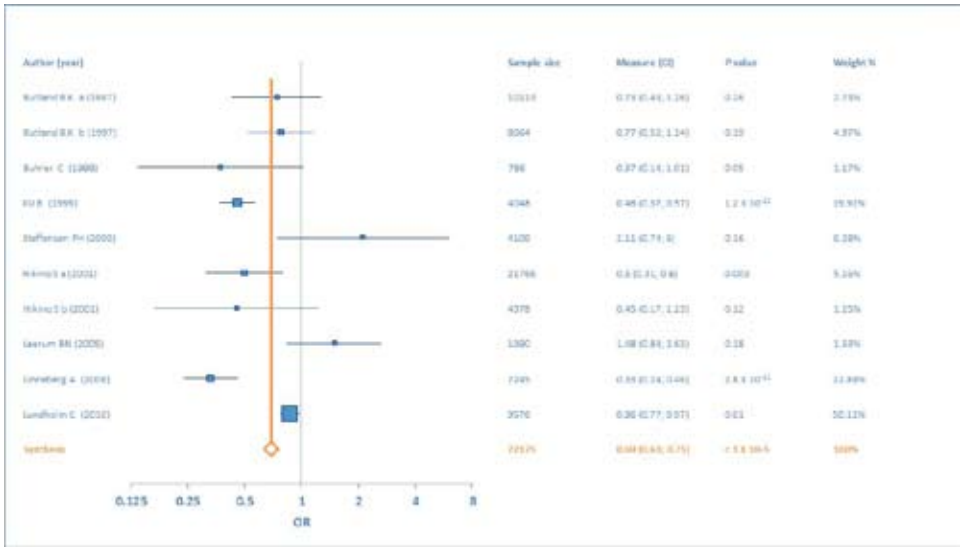

Figure 2. Meta-analysis of studies on low birth weight and atopic dermatitis.

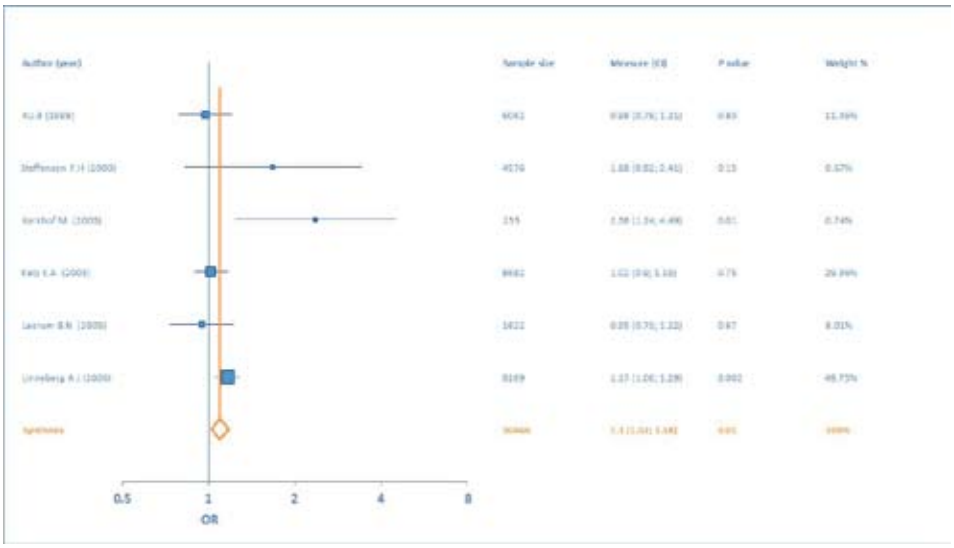

Figure 3. Meta-analysis of studies on high birth weight and atopic dermatitis.

calculated the odds ratio (OR) and corresponding 95% confidence interval (95% CI). Q test was used to assess heterogeneity. t^2 test was used to assess the variability between studies. Heterogeneity was also checked using the I^2 index. The value considered statistically significant was $P<0.05$. The data obtained was analyzed with the help of Mix 2.0.1.4. Pro (BiostatXL) software (6).

RESULTS

This meta-analysis gathered the existing data in the literature regarding the role of birth weight in the occurrence of atopic dermatitis.

We initially found 63 articles discussing birth weight and atopic dermatitis, however only 10 articles met our inclusion criteria for meta-analysis (Fig.1).

Out of the 10 articles, 8 articles were included in the meta-analysis of the association between low birth weight and atopic dermatitis, the number of patients with weight below 2500 g was not clear in two studies, since in these two articles low birth weight was defined as weight below 2970 g and below 3000 g (7,8).

In terms of meta-analysis of the association between high birth weight and atopic dermatitis, only 6 articles were included out of the 10. Two studies (9,10) had no data about subjects with high birth weight. In addition, in the studies by Butland (11) and Lundholm (12), high weight was not defined as weight over 4000 g; instead, patients with what we consider normal weight (patients with weights between 3000 – 4000 g were included in this category, so these studies were excluded.

Characteristics of included studies

Out of the 10 studies, 9 studies were carried out in Europe (2 in England, 2 in Denmark, 1 in Finland, Holland, Germany, and Sweden, and a multicentre study which comprised the northern countries: Norway, Denmark, Sweden, Island, and Estonia) and one study in Asia (Japan).

Low birth weight and atopic dermatitis

The meta-analysis of the 8 studies (9-16) on the relation between low birth weight and atopic dermatitis led to the conclusion that low birth weight represents a protective factor for the occurrence of atopic dermatitis (OR = 0.68, CI: 0.63 – 0.75, $P<0.0001$). The only study which concluded that low birth weight is a risk factor for atopic dermatitis is that of Steffensen, without being statistically significant (OR = 2.110, CI = 0.742-6.000, $P = 0.161$) (15). The studies with statistical significance are those of Lundholm (OR = 0.86, CI = 0.77-0.97, $P = 0.01$) (12), Linneberg (OR = 0.33, CI = 0.24-0.46, $P<0.001$) (14), Hikino (cohort of patients at 18 months) (OR = 0.5, CI = 0.31-0.8: p = 0.001) (10), Buhrer (OR = 0.37, CI = 0.14-1.01: $P = 0.05$) (9). The study with the highest statistical weight was by Lundholm (relative weight – 53, 65%) and influenced the final outcome of this meta-analysis the most (12).

High birth weight and atopic dermatitis

We carried out the meta-analysis of 6 studies that met the criteria of inclusion (7,8,13-16). The conclusion was that high birth weight represents a risk factor for atopic dermatitis (OR = 1.09; CI: 1.02 – 1.17; $P = 0.008$). The study with the greatest weight was that of Linneberg (relative weight 49.75) (14). The studies

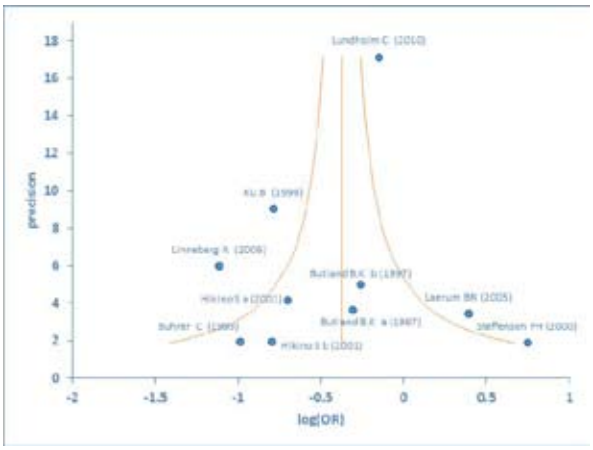

Figure 4. Funnel plot of studies on low birth weight and atopic dermatitis.

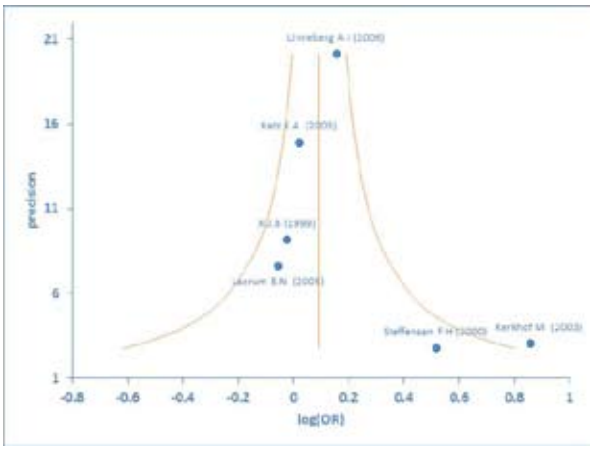

Figure 5. Funnel plot of studies on high birth weight and atopic dermatitis.

with statistical significance were those of Kerkhof (OR = 2.36 CI = 1.24-4.49; *P* = 0.009) and Linneberg (OR = 1.17, CI = 1.06-1.29; *P* = 0.001) (8,14).

Exploration of heterogeneity and publication bias

Following the funnel plot analysis for low weight birth (Fig. 4), five studies (12,13,14,15,16) where outside the distribution expected. Statistical analysis of heterogeneity showed moderate heterogeneity [Q statistic (63.84; $P = 2.41 \times 10^{-10}$), I-square (85.90; 95% CI = 75.93 – 91.74) and tau-square (0.125; 95% CI = 0.064 – 0.228)].

For high weight birth only one study was outside the distribution expected (Fig. 5). The analysis of heterogeneity showed [Q statistic (11.99; *P* = 0.033), I-square (58.38; 95% CI = 0 – 83.1) and tau-square (0.014; 95% CI = 0 – 0.05)].

DISCUSSION

This meta-analysis investigates the association between birth weight and the risk of atopic dermatitis. Our systematic analysis showed that low birth weight represents a protective factor for the occurrence of atopic dermatitis and that high birth weight is a risk factor for the occurrence of this disease. Previous studies evaluated the effect of birth weight on the atopic dermatitis occurrence, but our systematic review is the only one that analyses all the existent studies. The total number of subjects included in this meta-analysis was above 70000, which allows this study to draw conclusions without any concerns about low power due to sample size. Moreover, this meta-analysis contains studies from more than 10 populations with a medium heterogeneity, due to just two studies which are non-concordant with the rest. In addition, all studies with more than 5000 participants had the direction of the effect size concordant with the conclusion of our review, although some of them were not statistically significant. This allows us to speculate that the results of the two non-concordant studies were due to low power or to selection bias due to small sample size.

Although our methodology was carefully planned and followed during the study, and tried to take into account all the scientific aspects of the problem and to avoid biases, it was almost impossible to avoid some small limitations. One possible shortcoming of this systematic review was that studies which we introduced in this analysis did not comprise information about the gestational stage of the newborn. This is why a clear relation between weight and gestational age could not be done due to missing data in relation to gestational age of patients with low, normal, or high birth weight. However, this does not influence our conclusion. Another possible limitation was that patient classification depending on weight was quite varied; due to this, we excluded studies in which patients were not within the established weight parameters.

The mechanism through which birth weight could be involved in the occurrence of atopic dermatitis is not fully known. It is thought that high birth weight and post-maturity are associated with the increase of serum total Ig E, and post-maturity may be associated with the decrease in thymus weight and the balance between lymphocyte populations Th_1 and Th_2 of the thymus, in favor of Th_2 (17). A long period of exposure to Th_2 cytokines in pregnancy may predispose the fetal immune system to atopy (18).

In terms of the association between low birth weight and decreased prevalence of atopic dermatitis, there is no obvious explanation. One hypotheses was that the newborns with low weight usually need special care, so they stay within intensive care unit for a certain period of time, where they come into contact

with various antigens. Experiments done on mice emphasized the fact that continuous exposure to antigen doses determines the suppression of Th_2 lymphocytes and production of IgE (19). Usually, low birth weight is associated with prematurity, and possible precocious exposure to antigens determines the occurrence of tolerance rather than sensitization. This also explains the study by Steffensen, which is the only study where low birth weight represented a risk factor for atopic dermatitis. A possible explanation of this is the fact that this study included children born at full term with low weight, and did not include premature newborns.

CONCLUSION

The conclusion that can be drawn from this meta-analysis of existing studies is that low birth weight is a protective factor for the occurrence of atopic dermatitis, while the high birth weight is a risk factor for this disease. Further observational studies are needed to clarify this relationship, while also taking the gestational age into account.

ACKNOWLEDGEMENT

M. P. and N. M. P. have been supported by the Sectoral Operational Programme – Human Resources Development (SOP-HRD), financed from the European Social Fund and by the Romanian Government under the contract numbers POSDRU/89/1.5/S/64331 (M.P.), POSDRU/89/1.5/S/64109 (N.M.P)

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