# The Risk of Infectious Diseases Associated with Birth-weight: a Systematic Review and Meta-analysis

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**Abstract -**Birth-weight, a proxy indicator of intrauterine growth and development, has been reported to be linked to immune functions in later life. The relationship has only been assessed by individual studies with some conflicting reports. Therefore, this study carried out a systematic review, with meta-analysis, to gener ate evidence on the pos sible relationship between birth weight and r isk of i nfectious diseases in later life.

Databases, MEDLINE, PubMed, Goggle Scholar, CINAHL Plus, EBSCO Host, were systematically searched (from 1980-2016) to identify relevant original articles that assessed the relationship between birth-weight and subsequent risk of infectious diseases. We used random-effect model for the analysis, performed sub-group analyses and assessed publication bias.

For the systematic review, findings from 13 eligible studies were analyzed and all the studies except one reported significant relationship between birth-weight and risk of infectious diseases, even after some cofounders were adjusted. 184,560 data from studies included in the meta-analysis showed a significant increased risk of infectious diseases (OD=1.50; 95% CI: 1.26-1.80) when LBW (<2500g) was compared to with NBW (>2500g). Subgroup analyses revealed the study design as source of heterogeneity (Tau2=0.02; Chi2=13.27, df=1 (0.0003); I2=95%).

This study generated evidence on the inverse relationship between birth-weight and risk of infectious diseases in later life. There might be need for further research in developing countries - where LBW and infectious diseases are more prevalent. However, enhancing intrauterine development might be a promising strategy to tackle Under-5 infectious diseases morbidity and mortality.

## INTRODUCTION

Infectious diseases remain one of the leading factors contributing to the overall global burden of diseases [1], [2]; even though there were some erroneous beliefs that infectious diseases are already conquered. Published data has showed that infectious diseases were still responsible for the death of about 8.7million people globally [2],[3],[4], and a larger percentage involves children under five years old[4],[5]. Even in the developed countries – where there have been great decline in the incidence and prevalence of infectious diseases since the twentieth century [5], [6], [7]- the recent emergence of new infectious diseases such as Several Acute respiratory syndrome (SAR), and the re-emergence of some infectious diseases (cholera, dengue fever, Zika virus infection, Ebola and Meningitis) [1],[8],[9],[10], thought to have been eliminated, has heightened the concerns of the international community on prevention and control of infectious diseases.

Meanwhile, there is increasing evidence on the short and long-term impacts of intrauterine exposure. Studies have revealed that foetal growth, which is usually assessed through birth-weight, is closely associated with the risk of diseases such as type II diabetes, breast cancer, stroke, cardiovascular diseases, obesity and some minor diseases in infancy, childhood and adulthood [11], [12], [13], [14], [15], [16], [17]. The foetal programming hypothesis has been suggested as the underlying biological mechanism for this relationship [14], [15], [18], [19].

There is now some evidence that have suggested that the development and programming of immune system are influenced by the intrauterine life [20], [21], [22]. Babies that experienced intrauterine growth restriction (IUGR) – usually assessed by anthropometric measures such as birth-weight, birth length and ponderal index [23], [24] - were observed to be at higher risk of infectious diseases morbidity and/or mortality in later life [2], [20], [25], [26], [27], [28]. However, these findings are contested based on potential co-founding factors such as gestational age, socioeconomic status and environmental factors; and some studies have reported non-significant relationship [29], [30]. The aim of this study is to use the systematic review with meta-analysis approach to identify and appraise relevant studies to synthesize a pooled estimate of birth-weight effect on subsequent risk of infectious diseases in later life.

## METHODS

The guideline for conducting and reporting Meta-analysis of Observational Studies in Epidemiology (MOOSE) [31] was followed.

### Literature Search Strategy

The databases, MEDLINE, PubMed, Goggle Scholar, CINAHL Plus, EBSCO Host, were systematically searched (from 1980-2016) to identify relevant original articles that assessed the relationship between birth-weight and subsequent risk (morbidity and/or mortality) of infectious

diseases. In addition, snowballing was done; hence, the references of relevant articles identified during database search were searched manually. Search terms used were 'birth weight', 'foetal growth', 'low birth weight', intrauterine growth restriction, 'infectious diseases', 'risk of infectious diseases', 'hospitalisation due to infectious diseases', 'morbidity due to infectious diseases', 'mortality due to infectious diseases', 'cohort', 'case-control' without language limitation.

**Study Inclusion and Quality Assessment**

Studies were included into the systematic review if they met the following inclusion criteria defined a priori: original article must have assessed the relationship between the relationship between birth-weight and risk (morbidity or mortality) of infectious diseases, extractable data must be available for those included in meta-analysis, and it must be a published or and/or grey literature between 1980-2016. This was done to ensure findings are based on more recent data, thus, enhancing the validity of the study. In addition, inclusion was not restricted by study design or language of publication.

For the methodological appraisal, it was ensured that all included studies used the International Classification of Diseases (ICD) codes to diagnose infectious diseases. Further methodological assessment was done using AMSTAR – a measurement tool for assessing the methodological quality of systematic reviews. However, there were still some methodological limitations in some of the included studies but were considered while interpreting and discussing the findings (*See Fig 1 for the study selection process flow chart)*

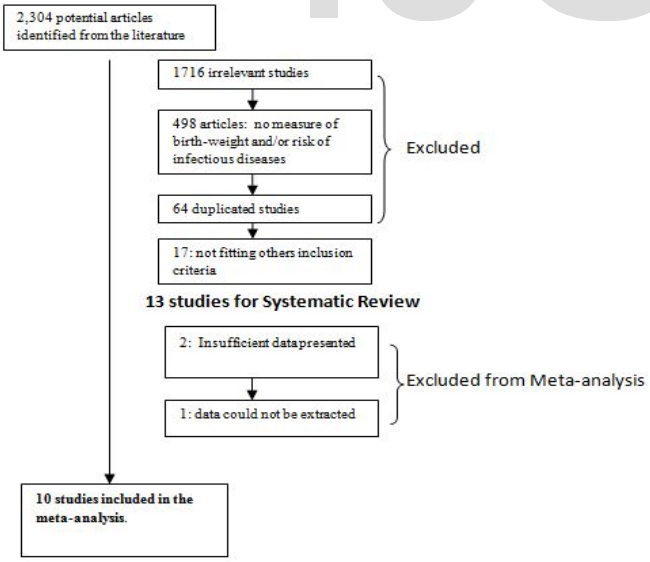


Fig 1: Flow diagram of selection process for studies on birth-weight and risk of infectious diseases

**Data Extraction and Data-analysis**

All the relevant data for both systematic review and meta-analysis was abstracted using a standardised form by the Principal Investigator (S.S). The meta-analysis, it involves a dichotomous comparison. Hence, the total number of subjects with LBW (<2500g) and NBW (>2500g) was extracted from all eligible studies and the number of subjects with risk (morbidity or mortality) due to infectious diseases was also extracted for each birth-weight group. This process was repeated twice by S.S and independently done by the O.S using the same standardised form; areas of differences were settled. (Supplement 1 for details of information and data extracted). In cases where there was some confusion or difficulties – especially in extraction of data - authors of the articles were contacted via email for clarifications.

In the data-analysis, qualitative analysis of the information and data abstracted was done after they were organised into emerging themes based on the risk of infectious diseases. In the meta-analysis, the Mantel-Haenszel method was used to combine the natural logarithm of the mean effect estimates across studies due to its robustness and higher precision in combination of weighted average32. Odd ratio (OR) at 95% Confidential Interval (CI) was used as effect estimate to measure and interpret the risk of infectious diseases in each of the birth-weight group (LBW and NBW). The random effect model was used due to the expected variability among the included study's methodology and for the fact that the random effect model account for both within and among variability.

Heterogeneity test was performed by visual inspection of the forest plot. In addition to this, statistical tests for heterogeneity namely chi-squared (X2/Chi2) and I2 test were performed according to Egger's test.

Sub-analysis was conducted in other to assess source of heterogeneity by stratifying the included studies for meta-analysis by their study design and risk of infectious diseases. In addition, sensitivity test was carried out in order to assess the influence of the chosen statistical model -Odd Ratio/Risk Ratio and Fixed Effect/Random Effect- on the result.

Finally, publication bias was assessed by the visual inspection and using asymmetry testing of funnel plot using the Egger's test.

All analysis was performed by using the Cochrane Library's Review manager (RevMan V.5.3) software.

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TABLE 1: BRIEF DESCRIPTION OF THE INCLUDED STUDIES

| Study (Author and Year) | Country | Study Design | Population Targeted | Follow-up Period | Data Source | Sample Size | Major Findings | Adjusted Cofounders |
|---|---|---|---|---|---|---|---|---|
| Hviid and Melbye, 2007 | Denmark | Cohort | Infants, Children and Adolescents | 1977 - 2004 | Danish Civil Registration System | 1.7 Million | Birth weight was inversely associated with risk of infectious disease hospitalization among children aged 0–14 years, the risk of hospitalization increased 9% for each 500-g reduction in birth weight (increase in rate ratio= 1.09, 95% CI: 1.09, 1.11). The effect was found to peak in infancy and to persist until 10 years of age | Age, calendar period, sex, birth order, mother's age at birth, degree of urbanization, nationality of mother, gestational age |
| Kadanla et al, 2009 | Malawi | Case-control | Infants | 2003-2005 | Maternity facilities of Chikwawa District Hospital and Montfort Hospital | 494 | LBW was not a significant risk factor for higher morbidity incidence of malaria, respiratory infection and diarrhea. | - |
| Person et al, 2014 | United States | Case Control | Infants | 2008-2009 | National Center for Health Statistics and Centers for Disease Control and Prevention | 3,843 | Infectious disease infant mortality ratio for LBW infants was higher (RR: 33.3, 95% CI: 31.1–35.7) than for NBW infants and was highest for VLBW infants (RR: 160.3, 95% CI: 149.4–172.1) | Sex, 5-minute Apgar score, maternal age (years), race, maternal marital status, Hispanic origin, and live birth order |
| **META-ANALYSIS STUDIES** | | | | | | | | |
| Reads et al, 1994 | United States | Cohort | Infants and Children | 1959-1966 | US Collaborative Perinatal Project (CPP) | 691 | Moderately LBW infants and children were at increased risk of infectious disease mortality (RR=2.49, 95% (CI) 1.74-3.55 | Gestational age, maternal age, education and race |
| Lira et al, 1996 | Brazil | Cohort | Infants | 1993-1994 | Prospective home visit data collection | 393 | The LBW infants (median 2380 gm) experienced a 7 fold higher mortality rate and 4 fold higher rate of hospitalization than appropriate birth weight infants | Gestational age and socioeconomic status |
| Samuelsen et al, 1998 | Norway | Cohort | Children | 1967-1989 | Norwegian Birth Registry and National Cause of Death Registry | 9,710 | The adjusted RR of death from all causes at ages 1-5 years was 2.18 (95% CI 1.85 2.56) for children with LBW as opposed to children with NBW. Death from infections, accidents, and other causes showed a reversed J-shaped association with birth weight | Gestation age, sex and maternal age |
| Yuan, 2001 | Demark | Cohort | Infants | 1984-1987 | National Hospital Registry | 10,393 | Result showed an inverse relationship between foetal growth and risk of hospitalisation with infectious diseases (P <0.05). | Gestational age, parent age, socio-demographic factors |
| Li, 2003 | United States | Case-control | Children and Adolescents | 1968-1996 | Washington State Birth and Death Records | 31,935 | Children with LBW (<1999) had greatest risk of overall childhood mortality [OR =1.7; 95% CI 1.5, 2.1]. LBW children experienced 2.5- to 2.7-fold increases in risk of infectious disease mortality among children <14 years of age | Sex, maternal age, race and marital status |
| Sorensen et al, 2004 | Demark | Case-control | Children | 1980-1999 | Danish National Registry of Patient, Birth Registry and Social registries | 39,098 | A persistent effect of LBW on the risk of meningococcal diseases was found in all age groups, with adjusted OR between 1.4 and 1.6. A reduced risk of meningococcal disease infection in the first year of life for children with a birth-weight of >3500 g (adjusted OR = 0.7, 95% CI: 0.6, 0.9) was found. | Gestational age, birth order and maternal age |
| Bari et al, 2009 | | Case-control | Infants | Neonatal period | Hospital records | 770 | The mean episode of morbidity among the LBW neonates was significantly higher than that of NBW neonates (0.09) (t=3.15, p-.002). | Controlled for gestational age naturally |
| Walters et al, 2009 | United States | Case-control | Adults | 1998-2007 | Washington (WA) State Comprehensive Hospital Abstract Reporting System (CHARS) and Washington State Birth Certificate database | 19,160 | LBW were more likely to be hospitalized for a respiratory illness as young adults (VLBW: OR=1.83; 95% CI: 1.28–2.62; P< 0.001; MLBW: OR=1.34; 95% CI, 1.17–1.53; P < 0.0005). | Birth year, sex, maternal age, race and marital status |
| Villamor et al, 2010 | Sweden | Cohort | Adults | 1926-1958 | Swedish Twin Registry (STR) | 21,596 | Tuberculosis risk was 11% lower for every 500 g of birth weight (P=0.05) | Sex, gestational age, birth year |
| Metzger et al, 2013 | United States | Case-control | Infants | 1987-2004 | Washington State Birth certificate and death | 50,814 | More infectious diseases hospitalization and mortality cases were found with low birth-weight (LBW, <2,500 g), very low birth-weight (VLBW,<1,500 g) infants | Gestational age, sex, maternal age and socioeconomic status |

## RESULT

Literature Search

The literature searches yielded 2,304 potential articles; only 21 studies were found to relate birth-weight with risk of infectious diseases. However, only 13 &10 out of these articles meet the entire inclusion criteria for systematic review and meta-analysis respectively (Supplement II for excluded studies).

### Characteristics of Studies

A total numbers of 13 studies - which involved total number 1,888,897 participants, were used for this review. 12 (92%) of the 13 included studies for systematic review reported an inverse relationship between birth-weight and risk of infectious diseases in later life while only 1 (8%) of the 13 studies reported an insignificant relationship. One of the 13 studies reported a U-shaped relationship while another one reported a J-shaped relationship.

8 (61%) of the included studies assessed infectious diseases morbidity and all the 8 studies except for one reported and inverse relationship between birth-weight and risk of infectious diseases morbidity. On the other hand, 4 (35%) of the 13 studies assessed infectious diseases mortality, while only one study assessed infectious diseases morbidity and mortality; all the studies reported an inverse relationship between birth-weight and risk of infectious diseases outcome assessed.

Furthermore, 7 (54%) of the 13 studies were used cohort study design in their methodology and all reported and inverse relationship between birth-weight and risk of infectious diseases. 6(46%) of the 13 studies were case control design and all except one study reported the inverse relationship.

Lastly, 5 of the included studies assessed risk of infectious diseases in relation to birth-weight in infants, 2 of the 13 studies assessed children exclusively, another 3 studies of the 13 assessed adult exclusively while 4 of the 13 studies assessed the relationship in infants and children. The age participation in this study ranged from 0-28yrs and included studies performed in Africa, America, Asia and Europe.

### Meta-Analysis of Risk of Infectious Diseases in Relation to LBW and NBW

Only 10 out if the 13 identified studies was eligible for meta-analysis *(See Fig 1)*.

LBW was found to be associated with higher risk of infectious diseases when compared to NBW (OR=1.50; 95% CI: 1.26-1.80 *See figure 1*). Visual inspection of the forest plot showed a marked heterogeneity and this was also confirms by statistical heterogeneity tests (Tau2=0.06; Chi2=58.36, df=9 (0.00001); I2=85%), hence, the random-effect model was used for this analysis. Nevertheless, the overall effect of birth weight (4.51) on risk of infectious diseases was also found to be significant at $p < 0.00001$ *(See figure 1)*.

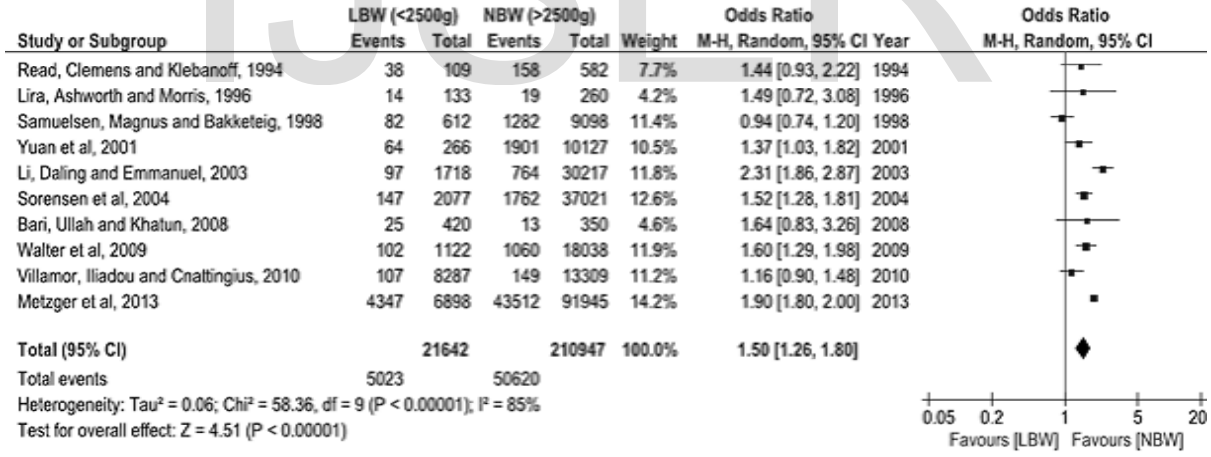


**Fig 2: Forest plot presenting the risk of infectious diseases in LBW and in NBW**. Studies were arranged according to their year of publication. The lines indicate the range of 95% confidential interval (CI) for each study. ORs estimate for each study's risk of infectious diseases was indicated by the black square and the size of the square indicate the statistical weight each study contributed to the overall estimate of the square. Lastly, the pooled odds ratio, which was represented by a diamond shape, was calculated with the random-effects method (1.50 95% CI 1.26-1.80).

### Sub-Group Analyses

In order to identify the source of the heterogeneity identified in the dichotomous analysis of LBW and NBW, sub-group analyses were carried out by stratifying the studies based on the risk of infectious diseases assessed and study design. Stratification by risk of infectious diseases assessed showed that neither the studies that assessed morbidity nor mortality were heterogeneous. However, stratification by study design showed that studies with cohort design had none significant heterogeneity among them (Tau2=0.01; Chi2=6.51, df=5 (0.26); I2=23%). While a significant heterogeneity was found among studies with case-control research design (Tau2=0.02; Chi2=11.22, df=3 (0.01); I2=73%).

More importantly, the test for the subgroup differences, which was done by using a random effects meta-regression,

showed that there is a high and significant level of difference between studies with cohort and case-control designs (Tau2=0.02; Chi2=13.27, df=1 (0.0003); I2=95%) *(See figure 3)*. However, the difference did not have significant impact on the pooled estimate as the result indicated that the risk of infectious diseases is significantly higher among individuals with LBW in both the cohort studies (OR=1.20; 95% CI: 1.02-1.41) at p< 0.03 and in the case-control studies (OR=1.81; 95% CI: 1.56-2.10) at p < 0.00001 (*See Fig 3*).

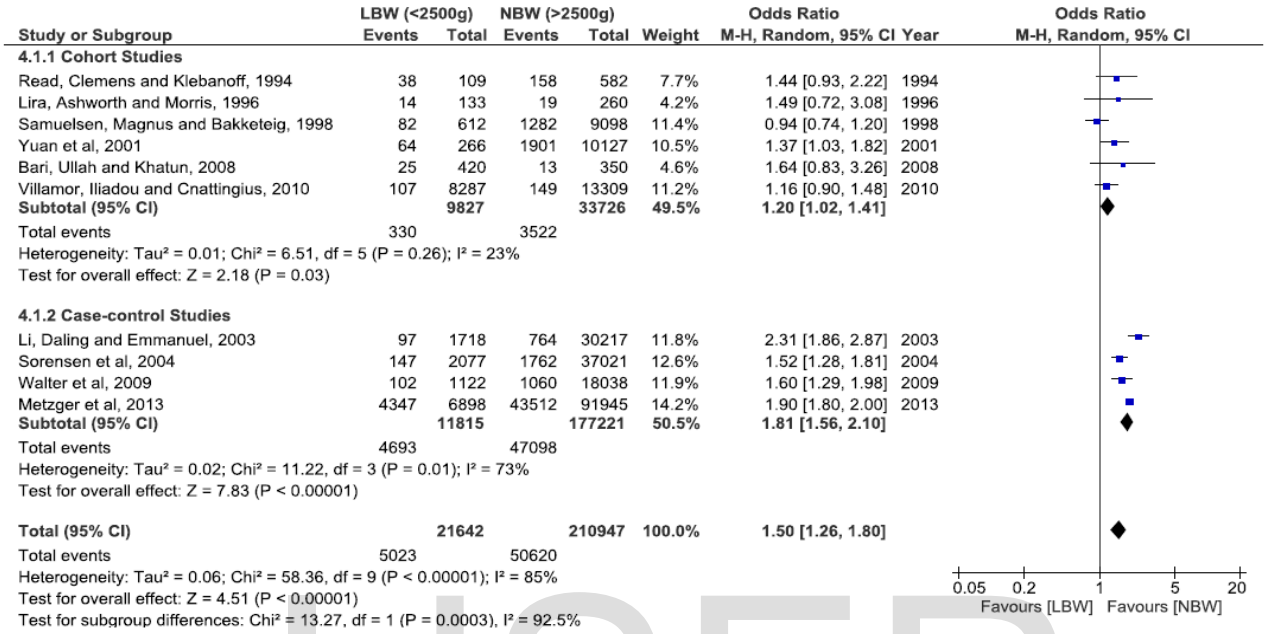


**Fig4**. Forest **plot for sub-group analysis: cohort and case-control meta-regression.** Studies were arranged according to their year of publication. The lines indicate the range of 95% confidential interval (CI) for each study. ORs estimate for each study's risk of infectious diseases was indicated by the black square and the size of the square indicate the statistical weight each study contributed to the overall estimate of the square

Finally, the publication bias assessment, which was done through visual inspection of the funnel plot, indicated that there was no publication bias in the study as the funnel plot was symmetrical (*See figure 2*).

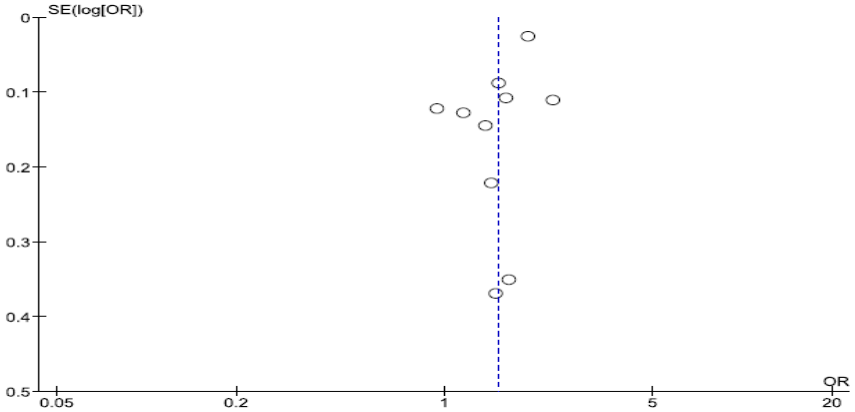


**Fig 3: Funnel plot of studies on risk of infectious diseases that measure LBW and NBW outcomes**. The standard error of the log OR is plotted on the vertical axis while the exposure (LBW) odd ratio is plotted on the horizontal axis. The funnel plot is symmetrical; indicating the absence of publication bias.

## DISCUSSION

This study qualitatively and quantitatively reviewed the possible relationship between birth-weight, as surrogate indicator of intrauterine exposure, and risk of infectious diseases in later life. All the articles systematically reviewed, except one, reported a significant inverse relationship birth-weight subsequent risk of infectious diseases. This relationship was found to be consistent irrespective of the study design used, the risk of infectious diseases measure, country of study and age group.

The findings from the meta-analysis on the risk of infectious diseases are based on the WHO classification of birth-weight groups. The analysis, which consist 232,589 participant data from ten observational studies, indicated that individuals with low birth weight (<2500g) are 1.5 times more likely to be at greater risk of infectious diseases when compared with individuals with normal birth weight (> 2500g) (see fig 1). The heterogeneity test in this analysis showed that there was a significant difference among the ten included studies (Chi2=58.36, df=9 (0.00001); I2=85%) *(See fig 1)*. Hence, a sub-group analysis (based on study design) was carried out in order to explore the source of this heterogeneity. The subgroup difference test showed that there was a marked difference between the two study design (cohort and case-control) Chi2=13.27, df=1 (0.0003); I2=95%) (See fig 3), thus, the difference in study design was identified as the main source of the observed heterogeneity. Interestingly, it was also observed that the strength of the negative association between birth weight and risk of infectious diseases was not influenced by the sub-group analysis (1.20 95% CI 1.02-1.41 for cohort studies and 1.81 95% CI 1.56-2.10 case-control studies) (See fig 3). This finding suggests that there is a strong and significant association between LBW (<2500g) and increased risk of infectious diseases.

Most of the studies from which the data were extracted reported similar findings on the inverse relationship between birth weight and subsequent risk of infectious diseases especially during infancy and childhood [30],[33],[34],[35]. Some other studies have also reported the same observation in adult life [27], [36],[37]. The largest of these studies, which directly assessed the relationship between birth weight and subsequent risk of infectious diseases [37], is a population-based case-control study of children during 1968-1996 in Washington, USA. It reported that the risk of mortality due to infectious diseases was almost three times higher among LBW children aged 1-19 years of age [OR =2.6; 95% CI 1.3-6.3]. A large cohort study of 1.7 million children further pointed to the adverse association between birth weight and risk of infectious diseases such as upper respiratory diseases, viral pneumonia, Septicaemia and diarrhoea throughout childhood. About 9% higher hospitalisation due to these infectious diseases for each 500g reduction in birth-weight was observed after controlling for confounding factors [32]. The limitation in this study is critical confounder could not be adjusted for; the socioeconomic status, however, it is a study with a very large sample size. Also, more recent large cohort study of about 22,000 twins in Sweden reported, that for every 500g increase in birth weight of monozygotic twins, there is a 46% lower risk of tuberculosis (95% CI, 1%-22%; P<0.05) [36]. The type of participants used in this study -monozygotic twins- enhanced the strength and reliability of the findings. This is because the difference in exposure to the intrauterine environment and maternal factors, which are potential confounders, are naturally controlled for in monozygotic twin studies [20], [38].

On the other hand, the data analysed in both articles [35],[36] and even in some other articles included in this study, were derived from cohort and populations that were about 60 years ago. Hence, the generalisability of these findings could be contested based on the argument that the recent improvement in prevention and control of infectious diseases, coupled with the reduced exposure to infectious diseases and improvement in health care systems might have affected the level of risk of infectious diseases in this contemporary period [39]. Nonetheless, findings from studies that analysed data from population in the 1990's and this early century have reported similar and consistent findings [27], [30], [34].

**Biological Explanation**

In health research, the biological mechanism that explains possible physiological processes for any observed relationship is highly important before a credible causal pathway can be established [40]. One of the strongest biological explanations for the relationship between birth weight and subsequent risk of diseases is based on a theory termed the developmental origin of health and diseases theory (DOHaD) - mainly propagated by Barker13. This theory stated that the intrauterine environmental exposure of a foetus, which is largely determined by maternal physiology, lifestyle and environment; usually have overwhelming influence on susceptibility to disease after birth and in later life[13],[41],[42].

Emerging evidence from growing body of literatures is now showing that some immunological pathways and immune systems are likely influenced adversely by deprived or suboptimum intrauterine exposure and thus, causing impaired immune functions after birth and in later life [26],[28],[36],[43],[44]. A case-control study [45], which involved 3,162 individuals from three rural villages in Gambia, has shown that individuals born during the hunger season, who are more likely exposed to deprived in utero environment, are usually at higher risk of nutritionally-mediated intrauterine growth retardation. It was further reported that about 200g-300g lower birth weight is associated with higher vulnerability to infectious diseases in adulthood. Due to the natural experimental scenario that the seasonal changes in Gambia allow; more observational studies have been carried out further to explore the impact of various intrauterine exposures on risk of infectious diseases. Findings have revealed alteration of immune function among babies born during the hunger season as they usually have smaller thymus size 43and

lower proportion of CD4+, CD8+ and low circulating leucocytes [46]. All these parameters are closely associated with immunity, hence, suggesting that the immune functions are likely programmed during intrauterine life.

Furthermore, studies conducted in Philippines and Pakistan has also reported findings that are consistent with the developmental programming of immunity. The former [47], which is a longitudinal study of 103 individual, reported that foetal exposure to under-nutrition is significantly associated with reduced thymopoietin production (P=0.006) and thus, suggesting the implication for immune-competence even till adulthood. While the latter study37 also reported a possible compromise of anti-body generation to polysaccharides antigen as the reason for the reduced antibody response to rabies and typhoid vaccination observed among low birth-weight participants of 257 adults cohort studies. Although both studies controlled for a range of confounders, yet their validity could be contested based on their relatively small sample size. However, findings from a study based on a large Danish-based cohort study of 10,400 new-born is consistent with the above results- although it argued that it is preterm birth, not necessarily IUGR, that is the major underlying factor for the relationship between LBW and risk of infectious diseases [36].

**Contribution to Knowledge and Strength of This Study**

This study has provided further evidence on the developmental origin of health and diseases (DOHaD) theory in relation to risk of infectious diseases. More specifically, this study has provided a more robust evidence on the in utero programming of the immune system; this is the first know study that has systematically assessed and quantify the level of risk of infectious diseases associated with birth-weight.

The strength of this study is greatly enhanced by the sample size of each studies included in the analysis as total of 232, 589 data was analysed. Furthermore, only cohort and case-control studies were included in the meta-analysis and a sub-group analysis based on the research design was performed. All the included studies reported the diagnosis of infectious diseases according to ICD codes, hence enhancing the methodology quality of this study. Lastly, all the studies that were included in the meta-analysis were from the western countries, especially from the Scandinavian countries, except for one of the study which is from a developing country. Therefore, it could be inferred that this study was majorly based on similar population; moreover, the findings remain unaffected even when the study carried out in developing country was unchecked for sensitivity test.

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**Implication and Recommendation for Policy and Practice**

The relationship between sub optimum birth-weight and increased risk of infectious diseases as confirmed in this systematic review with meta-analysis study further emphasised the importance of foetal life, intrauterine environment and foetal growth in relation to susceptibility to diseases in later life. It has been established that birth-weight is the most commonly used surrogate indicator of foetal growth and intrauterine life [49], therefore, the findings from this study have implications for both developed and developing countries where LBW is associated with preterm birth IUGR respectively [50]; foetal growth is interrupted in both situations irrespective of the underlying cause. Therefore, policies and practices targeted at preventing foetal adverse exposure by promoting maternal health during pregnancy might be a promising to tackle infectious diseases among children.

**Limitations**

In this study, sub-analysis studies based on duration of gestation, foetal growth rate and socioeconomic status could not be performed because most studies did not separate data on these factor, therefore, they could not be extracted. These analyses could have helped to give more precise details into the relationship between birth-weight and risk of infectious diseases. Furthermore, the proxy nature of the outcome measured in most of the studies could be a limitation; as most of the studies either measured mortality due to infectious diseases or hospitalisation due to infectious diseases. These will only covers severe conditions, therefore, some data on risk of infectious diseases might not be accurate.

**CONCLUSION**

This study revealed that there is 1.5times higher risk of infectious diseases in individual with LBW, especially during infancy and childhood. Therefore, birth-weight might be a useful indicator of intrauterine processes that influences immune functions and risk of infectious diseases in later life.

**ACKNOWLEDGEMENT**

The Risk of Infectious Diseases Associated With Birthweight- A Meta-Analysis Study "None"

**STATEMENT OF INTEREST**

The Risk of Infectious Diseases Associated With Birthweight- A Meta-Analysis Study "None"

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