Effect of birth weight on adulthood renal function: A bias adjusted meta-analytic approach

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ABSTRACT

While the association between low birth weight (LBW; <2500 g) and development of adult chronic renal disease (CKD) is inconsistently reported, less information is available regarding association of high birth weight (HBW; ≥4000 g) with CKD. We undertook a systematic review and meta-analysis on studies published before 30 September 2015 and report associations between birth weight and renal function. Blood [Glomerular filtration rate (GFR)] and urine [Microalbuminuria/Albumin excreation rate (AER)/urinary albumin creatinine ratio (ACR)] parameters were used to define CKD. Three different effect size estimates were used (odds ratio, regression coefficient, and mean difference). The odds of developing CKD in the life course among those born LBW was 1.77 (95% CI:1.42, 2.20) times and 1.68 (1.27, 2.33) times, assessed by blood and urine parameters respectively. Higher risk was also observed among Asian and Australian populations (blood: OR 2.68; urine: OR 2.28), individuals aged ≤30 years (blood: OR2.30; urine: OR 1.26), and ≥50 years (blood: OR 3.66; urine: OR 3.10), people with diabetes (blood: OR2.51), and aborigines (urine: OR 2.32). There was no significant association between HBW and CKD. For every one kg increase in BW, the estimated GFR increased by 2.09 ml/min/1.73 m^2 (1.33-2.85) and it was negatively associated with LogACR (ß-0.07, 95% CI: -0.14, 0.00). LBW inborn had lower mean GFR -4.62 (-7.10, -2.14) compared to normal BW. Findings of this study suggest that LBW increased the risk of developing CKD and HBW did not show any significant impact.

INDEX WORDS: Birth weight**,** renal function, systematic review, meta-analysis

INTRODUCTION

Over the last decades, the burden of chronic disease has increased at an alarming rate [1-4]. Evidence from the recent past shows increasing prevalence of kidney disease, which has adversely affected the health system as well as imposing an enormous social and community burden globally irrespective of country economic status [5, 6]. Several epidemiological and experimental studies suggested that most of the chronic diseases including chronic kidney disease (CKD) are linked with in utero life as first stated by Barker's hypothesis of "early origins of late disease" [7]. This is supported by Bernner's hypothesis, which proposes that an inborn nephron deficit due to intra-uterine growth retardation (IUGR) or low birth weight (LBW) predicts long term risks of hypertension, renal impairment or decreased glomerular function, age adjusted glomerulosclerosis and later CKD or end stage renal disease (ESRD) [8]. Moreover, further adverse events during extra-uterine life or life style during pregnancy may exacerbate the ramifications on renal function resulting in CKD [9].

The association between LBW and CKD is not consistent due to heterogeneity in age of diagnosis, geographical diversity and ethnic variation. Moreover, use of different biomarkers and formulae to determine CKD might also contribute to heterogeneity [10]. Usually, glomerular filtration rate (GFR) is one of the easiest methods; but the use of different formulas and different biomarkers for example serum creatinine, serum cystatin are still of great concerns [11]. Further, microalbuminuria is also a well-recognized biomarker for early prediction and diagnosis of CKD [12].

White SL et al. in 2009 made an attempt to harmonize such inconsistencies by including findings of all studies published before January 2008, and estimated the risks of albuminuria,

ESRD and low estimated GFR (eGFR) as odds ratios (ORs) of 1.81, 1.58, and 1.79 among respectively newborns with LBW [10]. However, the study used traditional methods without controlling for heterogeneity across studies and reported the outcomes only in OR as a measure of effect size. Another review by Rong XU et al. in 2010 examined the role of LBW in pathogenesis of CKD and included studies which reported mean difference of GFR between LBW and normal weight as control [13]. This study also had similar methodological limitations.

Recent studies consistently found that HBW increased obesity or metabolic risk irrespective of age and sex, which is explained by the over-nutrition hypothesis [14, 15]. This might suggest that HBW is likely to increase the risk of CKD through the obesity pathways. However, no such associations have ever been described for newborns with high birth weight (HBW) and the available analyses do not consider the linear associations between LBW and renal function using different biomarkers. Thus, the present appraisal aimed to determine the pooled estimation of association of birth weight (LBW and HBW) with CKD by using different biomarkers (blood and urine), including a variety of estimates of effect sizes and models. Moreover, we also aimed to determine the at risk population by including other factors such as geographical diversity, age differentials, effect of underling predictors such as diabetes and hypertension and ethnic difference.

METHODS

Search strategy

A systematic review of all published study findings irrespective of age, sex and ethnicity was undertaken in accordance with preferred reporting items for Systematic Review and meta-analysis guideline in PubMed (www.ncbi.nlm.nih.gov), Embase and Scopus till October 28, 2015. We searched for articles examining the association of birth weight and renal failure (chronic kidney disease) across different age groups. To search the articles no limits were inserted and references from the relevant literature were hand searched and used to identify additional relevant studies. The key words used for searching were, "*birth weight, low birth weight/LBW, infant-low birth weight, high birth weight, foetal/fetal growth retardation, intrauterine growth retardation or IUGR, foetal/fetal development, small for Gestational age/SGA*" with "*kidney, renal, kidney function, renal function, kidney failure, renal failure, kidney disease, renal disease, kidney function impairment, renal function impairment, chronic kidney disease/CKD, glomerular filtration rate/GFR, glomerular filtration, proteinuria*". We retrieved 15,565 articles and based on the information related to topic, abstract and full-text articles, a total of 15,514 studies were rejected, as they clearly did not meet the inclusion criteria (see below). A total of 51 studies were finally included for this study. The search strategy is described in detail in the online appendix.

Inclusion and exclusion criteria

Studies were included if they: 1) were published in the English language; 2) used the following study designs - cohort, case-control, cross-sectional, randomized control trial; 3) included people of any age >1 year, sex and ethnicity; 4) assessed the association of LBW with CKD by odds ratio, regression co-efficient and mean difference. The exclusion criteria were: 1) case reports, qualitative reports, comments, letters and reviews 2) animal or experimental models, 3) renal impairment or assessment of renal function as neonate and less than one year, and 4) other renal pathology such as minimal change nephropathy, immunoglobulin A nephropathy, and nephritic syndrome.

Data extraction and quality appraisal

A standard data extraction form summarizing the study design and other relevant raw data was completed for each article by an independent reviewer following PICOS guideline [16] (**Table S1**). Studies reporting their outcomes in odds ratios were synthesized. In some cases the effect sizes were transformed, that is converted into odds ratio (OR) when the necessary data for calculation were available. Data synthesis was also undertaken for standard error (SE) and standard deviation (SD) among studies with linear association or mean difference. A quality-scoring instrument (**Table S2**) was developed based on standard bias criteria for observational studies to adjust for study deficiencies. **This instrument meets the criteria of New Castle Ottawa score (selection, completeness and outcome) for both cohort and case-control studies [17, 18].** Following the standard procedure quality scoring was done by two reviewers. Any disagreement in the scoring was resolved by consensus and each item

that was not deficient was given a point. These were then summed to form a univariate quality score (**Table S3**).

Primary analysis

Three different outcomes have been measured: 1) estimation of risk by Odds ratio; 2) estimation of linear association by regression coefficient; and 3) estimation of risk by mean difference. Pooled estimations were equated for each outcome based on assessment of renal function by two biomarkers separately: blood (eGFR) and urine [Microalbuminuria/Albumin excretion rate (AER)/urinary albumin creatinine ratio (ACR)]. To adjust for bias, the pooled estimates were obtained using three different meta-analytic models, given that the random effects (RE) model [19] is known to underestimate the statistical error which could lead to overconfident results [20-22]. Two other statistical approaches were used - the bias adjusted quality effects (QE) model [17] and its bias unadjusted variant called the inverse variance heterogeneity (IVhet) model [23]. The quality effects (QE) model adds a synthetic bias variance based on relative quality ranking. However, both the QE and the IVhet models use quasi-likelihood based variance structure without distributional assumptions and thus have coverage probabilities for the confidence interval (CI) well within the 95% nominal level. Both have been documented to have a better performance when compared to the RE method [23]. Heterogeneity was determined to be present when the value of τ^2 was greater than zero and/or the Q-statistic was significant at a $P < 0.10$ [24]. All analyses were done using MetaXL version 2.0 [25].

Sensitivity analysis and publication bias

Sensitivity analyses were performed with the aim to evaluate the robustness of our meta-analysis by changing selection criteria of the studies based on their regional difference, age of assessment (<30 years, 31-50 years, and 51 and above years), presence of potential predictors such as diabetes, and ethnicity variation. Finally, analysis of the effect of potential unpublished studies was undertaken to evaluate the possibility of publication bias within this meta-analysis. Publication bias was assessed via funnel plots as well as Peter's regression (when the effect size was calculated in OR) and Egger's regression. For Peter's and Egger's regression, asymmetry of the studies was considered if the intercept of regression deviated from zero with P <0.10 [26].

RESULTS

Study characteristics

Overall characteristics

A total of 51 [27-77] relevant papers finally met the inclusion and exclusion. Of them, 36 followed a cohort design [27-30, 32, 34, 36-44, 46-53, 56, 57, 59, 62, 63, 66, 67, 71-77], nine a case-control design [31, 35, 45, 54, 58, 60, 61, 64, 69, 70] and five were of cross-sectional design [29, 33, 55, 61, 65] while one was a randomised control trial [68]. Most of them collected birth weight retrospectively by chart-review with only 4 studies collecting birth weight prospectively [37, 39, 50, 62] from birth records. One recorded self-reported [30] birth weight and three did not mention their methodology [43, 54, 60]. Eight studies included patients attending hospitals or clinics where they were enrolled [37,

[45, 56, 61, 66, 67, 71, 74], while the remainder were community based. One community based study was conducted among kidney donors [52]. A total of 2269188 individuals were assessed, including a single study from Norway [47] which comprised a population of more than 2 million. A total of three studies were conducted among aboriginal populations: two from Australia [29, 40] and one from Canada [49]. Considering the age of assessment of renal function, 22 studies assessed renal function at less than 30 years [28, 32, 33, 36, 40, 42, 43, 46, 47, 51, 54, 55, 58-62, 67, 70, 73, 74, 77]. Of these 11 were at paediatric and adolescent age group [33, 40, 43, 51, 55, 60-62, 73, 74, 77]. On the other hand, there were five studies that had assessed renal function at aged 50 years and above [34, 45, 48, 50, 52] and the rest were at middle age (30-50 years). Four studies did not mention age clearly [35, 56, 72, 76]. Two studies included twins [57, 59]. In total 438 monozygotic and 287 dizygotic twins were studied. Most of the studies either used blood or urine parameters to assess renal function; while only four studies analysed both specimens [36, 44, 50, 55]. Blood was used for estimation of GFR to define CKD or ESRD [31, 35, 38, 41, 42, 44, 45, 47, 52, 76] from serum creatinine; while microalbuminuria was used to determine CKD from urine to estimate urinary albumin creatinine ration (ACR) [27, 29, 32, 33, 36, 37, 39, 50, 52, 53, 55-57, 62, 68, 72] and albumin excretion rate (AER) [28, 34, 39, 40, 43, 65-67, 69, 74] to ascertain the association with birth weight. Moreover, five studies reported very low birth weight [36, 55, 58, 60, 62].

Studies estimated the risk of CKD or ESRD, and mean difference, most of them considered newborns with birth weight <2500 g and compared with those of normal birth weight (2500-3999 g). However, one study estimated ponderal index (lower 3rd percentile) [34], two studies estimated birth weight percentile [39, 42] and one study considered intra uterine growth retardation [62]. Ten studies reported the association between HBW and CKD [27, 31, 35, 38, 39, 43, 44, 47, 49, 54].

Study quality

Of 36 studies included in meta-analysis, 21 estimated the effect size in OR [27-35, 37-41, 43-45, 47, 49, 52, 54], six studies estimated regression coefficients [36, 46, 48, 50, 51, 53], eight studies measured as mean difference [55-62], four of the studies estimated both OR and mean difference [29, 32, 39, 52], one study reported both OR and regression coefficient [42], one measured both mean difference and regression coefficient [36]. Four studies used cross-sectional samples [29, 33, 55, 61] and six were case-control [31, 35, 45, 54, 58, 60] study designs, suggesting a possible source of design-specific bias. Most of the studies had well documented study designs and inclusion criteria except for two studies that reported this poorly [29, 40]. Six studies examined confounding factors extensively (≥7 confounders) [37, 43, 44, 47, 50, 52], while 13 studies did not include any confounding factors [28, 29, 35, 41, 46, 49, 55-58, 60, 62, 74] and the remainder of the studies included one to seven confounders to measure the association. Only eight studies were conducted in populations with diabetes and/or hypertension and/or family history of CKD, diabetes, or hypertension [27, 28, 34, 38, 39, 43, 44, 50]. Only seven studies estimated risk or association adjusted for single maternal factors (gestational age [39, 51], maternal diabetes [42, 43, 53], maternal BMI [53, 54]). One study included four factors for adjustment (maternal age, diabetes, preeclampsia and renal function) [42] and another study considered three factors (age, marital status and preeclampsia) to measure the association between birth weight and renal function [47]. Two studies considered the behavioural factor of smoking [37, 48]. All but four studies [30, 43, 54, 60] recorded documented (birth record) birth weight. Studies estimating risk for CKD used standard cut-offs [either eGFR (<60 ml/min/1.73 m2) or ACR (≥30 g/mol)]; however, some studies considered CKD by ACR ≥2.5 g/mol [37, 39, 49] and four considered AER >15 g/mol [28, 34, 39, 43], while four studies assessed ESRD [31, 35, 38, 47]. The quality was assessed for all the studies individually, and the corresponding quality scores are shown in Supporting

Information Table S3. The quality assessment was summed into a univariate score with a maximum of 15 points and studies ranged between 4 and 15.

Meta-analysis

Newborns with LBW were at 1.77 (95% CI: 1.42, 2.20) and 1.68 (1.27, 2.33) times higher risk of CKD in later life assessed by blood and urine respectively (Figure 2). On the other hand, in newborns with HBW, overall risk of CKD at adulthood was 1.09 (0.91-1.32) times higher than normal birth weight individuals and for blood it was 1.04 and for urine 1.11 (Figure 3).

Two pooled linear estimations were undertaken due to heterogeneity across studies in measuring renal function. Firstly, for eGFR, every 1 kg increase in birth weight was positively associated with a change in eGFR of 2.09 ml/min/1.73 m^2 (95% CI: 1.33, 2.85). On the other hand, log transformed ACR was significantly and negatively associated [-0.07 (-0.14, 0.00)] with birth weight (Figure 4).

Two separate pooled estimates were calculated for GFR and ACR to determine mean differences. The pooled estimate for GFR revealed that individuals with LBW had lower mean GFR 4.62 ml/min/1.73 m^2 (95% CI: -7.10, -2.14) compared to their counterpart with normal birth weight (Figure 5). However, lower mean ACR 1.09 (-2.32, 0.14) was found among individuals with LBW, which was not statistically significant.

In sensitivity analyses, Asians and Australians were at greater risk (OR: blood - 2.68; urine - 2.28) compared to Europeans (OR: blood - 1.85; urine - 1.56) and individuals from USA and

Canada (1.59; 1.64) (Table 4). Individuals aged above 50 years were at higher risk (3.66; 3.10) compared to middle aged participants (31-49 years). However, higher risks were also observed among the young adult and paediatric age group (2.30; 1.26) compared to middle age (30-49 years) participants. Individuals with diabetes were at higher chance of developing CKD compared to non-diabetic people as assessed by blood (2.51 vs. 1.85) (Table 4). LBW aborigines were at higher risk of CKD in adulthood compare to non-aborigines (2.32 vs. 1.50) assessed by urine only (Table 4).

Publication bias

The funnel plots were symmetrical (for all the studies which measured the risk in OR, linear association and mean difference) suggesting no publication bias. Further, Peter's regressions for OR were examined and publication bias was not found for LBW with CKD for blood (regression coefficient: 0.001; *P* =0.03) or for urine (regression coefficient: 0.002; P=0.04). For HBW there was some evidence of bias (regression coefficient: <0.001; P=0.07). The intercepts for the association between BW and GFR (-0.020; P=0.96) and ACR (0.025; P=0.36) on Egger's regression also included zero, suggesting absence of publication bias in the studies included in this meta-analysis. Therefore, publication bias does not appear to be an important consideration for this study. On the other hand, regression coefficient for mean difference for eGFR (2.21, p=0.004) and ACR (0.70; p=0.020) indicated presence of publication bias.

DISCUSSION

Predisposition towards pathophysiological changes in smaller or immature kidneys includes lower numbers of nephrons at birth or early loss of nephrons. Later (mal) adaptive mechanisms include increased capillary pressure and glomerular hypertrophy resulting in intraglomerular hypertension which accelerates nephron attrition and progression towards CKD among newborns with LBW [8, 78, 79]. In the present study, inborn with LBW were at 1.77 and 1.68 times higher risk for CKD compared to normal birth weight newborns, which is consistent with the previous study published in 2008 [10] that reported increased odds of 1.73 with both combined blood and urine measures. We found both blood and urine analyses have similar sensitivity in detecting renal impairment, whilst urine analysis has potential practical advantages, as it is a non-invasive and cost effective method.

Newborns with HBW are also at 1.09 times higher risk of CKD at later life, though the association is not statistically significant. We found ten studies which ascertained the association between HBW and CKD [27, 31, 35, 38, 39, 43, 44, 47, 49, 54]. Only one study) among Pima Indians with diabetes) showed high odds ratio for CKD, which did not appear representative of the general population [27]. This might be due to intrauterine diabetes exposure as reported by Nelson [27], as HBW may be associated with later development of autoimmune disease [80-82], metabolic syndrome [14] and ESRD due to diabetic nephropathy [31]. Alternatively, it might be linked with sustained excess weight gain leading to overweight and obesity. A recent review among individuals with renal disease reported an association between childhood obesity and increased risk of onset renal disease [83]. Several other longitudinal studies also demonstrate an association between obesity and incidence of CKD at adulthood especially among adults [50,

[84]. Moreover, association with overweight first detected at a younger age with increased risk of CKD had also been documented [85].

We also estimated other pooled associations between birth weight and renal function such as linear association (beta coefficient), and mean difference. In all cases, the magnitude of association between birth weight and CKD was also similar to that of risk estimation between LBW and CKD. For example in the linear model, every 1 kg increase in birth weight was positively associated with change in eGFR of 2.09 ml/min/1.73 m^2. Considering mean difference, newborns with LBW had lower GFR by 4.62 ml/min/1.73 m^2 compared to their counterpart with normal birth weight which is higher than the previous estimation done by Rong XU in 2010 [86].

LBW newborns from Asia and Australia appear to be more at risk of CKD compared to European, and American and Canadians. Recent studies show that the prevalence of CKD has been increasing in most of the Asian countries. Taiwan, Japan, South Korea, Malaysia and India are within the top 20 countries globally with highest annual incidence of CKD [6]. A study from Singapore also reported higher odds (2.09) of CKD among 6^{th} grade school children with LBW [33]. A study from Japan has also demonstrated a positive correlation between the annual incidence of LBW and of ESRD [76]. Such correlations could not be estimated for other Asian countries, perhaps due to poor national birth registration systems as well as unavailability of life course health status registers [87]. However, prevalence of LBW is 15% based on available records of birth weight in developing and least developed countries, with higher prevalence (25%) in South Asians according to UNICEF [87]. On the other hand, among the Australian population the odds of CKD among LBW individual in adulthood was also higher. According to the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) the

prevalence of CKD among the general population over the last decade increased from 4% to 5% (20% percent increase) with an incidence of impaired eGFR of 0.4% per year [88].

Food contamination is currently a great public health threat, especially in developing countries. As the kidney is the main organ responsible for extracting and eliminating all the consumed health hazardous additive chemicals [89], resultant hyper activation of the glomerular membrane and toxic sedimentation might alter the renal homeostasis. Moreover, unplanned urbanization reduces open space, which compounds the risks of sedentary lifestyle and lower physical activity. These factors, in addition to environmental pollution may also increase the risk of diabetes and hypertension. Diabetes accelerates progression of vascular disease and carries a substantially increased risk of renal failure, while hypertension causes nephrosclerosis. Thus, both diabetes and hypertension are major predictors for renal impairment and the development of CKD. In the present study, odds of CKD were higher among diabetics compared to non-diabetics born with LBW. Among Australians, diabetes itself is responsible for 35% of all newly diagnosed ESRD, whereas hypertension and atherosclerosis account for 15% [88]. It has also been observed that aboriginal LBW newborns in Australia [29, 40] and Canada [49] are at higher risk of CKD in later life, which once again strengthens the evidence for vulnerability to chronic disease in these populations as reported elsewhere [90, 91].

Age of onset of CKD is another area of controversy due to inconsistency in the assessment of renal function. Though CKD is thought to a disease of older age due to degenerative changes and organ malfunction, young children born with LBW are also at greater risk [33, 40, 51, 55, 60, 61, 73, 74, 77]. It is difficult to precisely explain the complex relationship between the pathway(s) potentially connecting LBW and CKD in early life and young adulthood, and to define which

specific factors contribute to disease progression **mostly due to different causes of CKD in children and adult**. **Evidences showed higher albuminuria may depends on ethnicity [29, 32, 64], high blood pressure [92] due to raised natriuresis (also hormone or hormone like substance involvement [93]) or alteration of Na^+/K^+-ATPase activity [32]. Change in body weight with environmental exposure and relationship between LBW with early onset of other metabolic disorder for example diabetes [94] in addition lower number of nephrons might be alternatively speculated the relation of LBW with CKD among pediatric and early adult age groups; however, further studies are needed in this area**. However, interestingly no evidence of CKD was found among kidney donors with LBW [52]. This could be due to post donation well-maintained life-style and behaviour or selection pre donation for overall health and normal renal function. A significant relationship has also been reported between LBW and ESRD among females [35]. This could be biologically based - sex differences in kidney size and BW with CKD have reported elsewhere [44]. However, such a differential might also be caused by creatinine-based sex adjusted estimation of GFR formulae [95]. Conversely, a significant association between LBW and CKD was reported only among males by Li S et.al. [44].

Maternal pre-pregnancy and pregnancy events, and life-style and behavioral factors such as diabetes, eclampsia or pre-eclampsia; smoking and alcohol consumption are important predictors which are recorded in only 3 studies. All of these are not merely confounders but also may be intermediate factors in the causal pathway of compromised organogenesis in utero and incipient nephropathy in offspring at adulthood reported elsewhere [28]. Only a few studies have estimated the risk of CKD by adjusting for the participants' life-style and behavioral factors [37, 42, 48]. Moreover, maternal nutrition during gestation (especially under nutrition) has been linked to impaired renal function in the twin offspring. For example, as

reported by Painter RC [37], mid trimester Dutch pregnant mothers who were exposed to famine had higher rates of offspring microalbuminuria at age 50. Positive associations between intra-pair differences in size at birth and subsequent intra-pair differences in creatinine clearance in later life suggest that the relationship between birth weight and subsequent kidney function is robust to confounding by maternal and early life factors. However, no significant increase in the prevalence of microalbuminuria or albumin excretion rate was observed for individuals exposed to intrauterine maternal starvation during the 3-year siege of Leningrad [50]. Moreover, maternal obesity is also associated with malformations of offspring urogenital system [96] which again could be related with maternal diabetes though the findings are not consistent [97].

STREGTHS AND LIMITATIONS

Retrospective collection of birth weight from a record in most of the studies accentuated the chance of misclassification bias due to uncertainty in availability of valid records from all the study participants as well as lack of opportunity to compare with individuals without any record. Limited availability of information regarding maternal pre-pregnancy and pregnancy events are other concerns. Only 3 studies considered such potentially important information– especially relating to diabetes and eclampsia [42, 43, 47]. Such information was also lacking for study participants. Moreover, age of assessment, study designs other than longitudinal study, risk estimation by odds ratio, use of different biomarkers for defining CKD were other limitations. Despite all of these potential limitations, the use of biomarker based independent analysis, the use of three different effect size estimates to determine associations between LBW and CKD, the use of three different models for pooled estimations as well as several sensitivity analyses with extra effort for controlling bias were the strengths.

CONCLUSIONS

Findings from the present study indicate a relationship between LBW and CKD. Newborns with LBW are at greater risk of developing CKD or impairment of renal function in adulthood. The causal relationship could be linked with organogenesis. Lack of information regarding maternal, perinatal and antenatal lifestyle and behaviour and the offspring's' socio-demographic indicators at adulthood, limits definitive conclusions. However, the progression of renal impairment in LBW newborns is still of great concern, even after identifying potential confounders. Given the epidemic of diabetes and our finding that at least one-third of people with diabetes experienced CKD and LBW, this risk is of great importance. Further, prevalence in Asia is particularly high and diabetes is also associated with social disadvantage people as seen in aboriginal groups. LBW needs to be examined in conjunction with other risk factors and diseases such obesity, hypertension, and coronary heath disease in terms of its relative contribution to later renal disease. Moreover, the potential association between HBW and CKD, though not significant in this meta-analysis, needs to be explored in detail given the progression of the global epidemic of overweight and obesity.

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CONFLICT OF INTEREST

The authors have declared that no competing interest exists.

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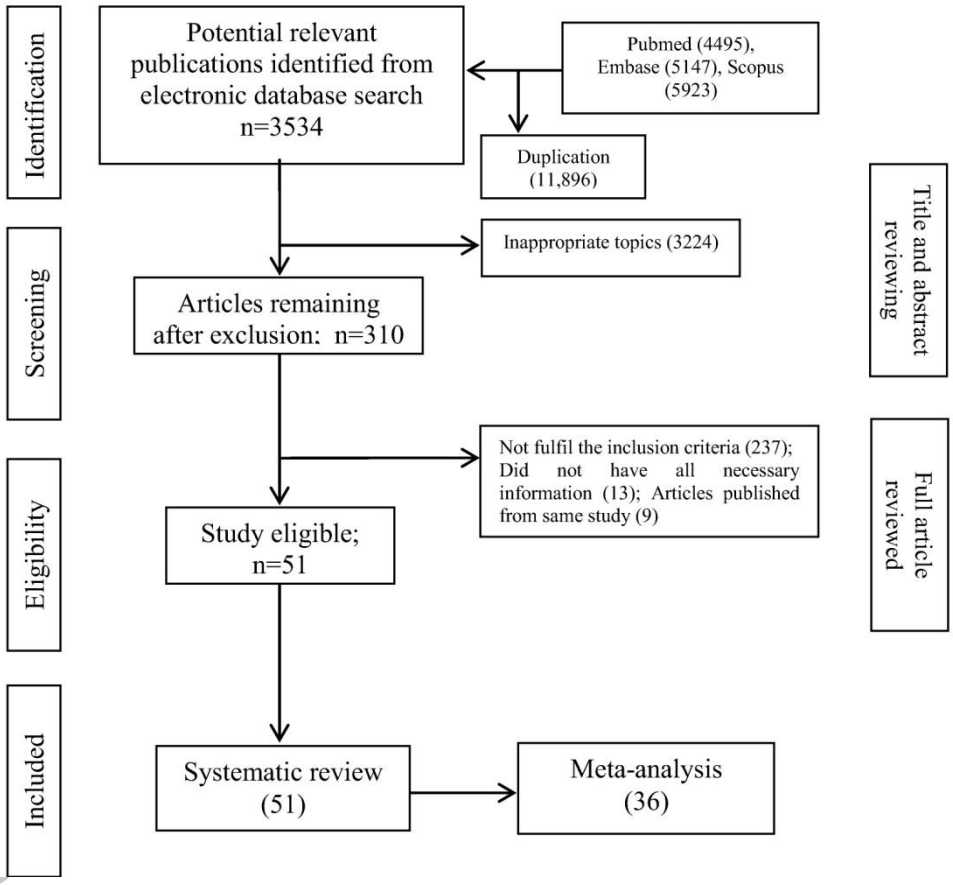
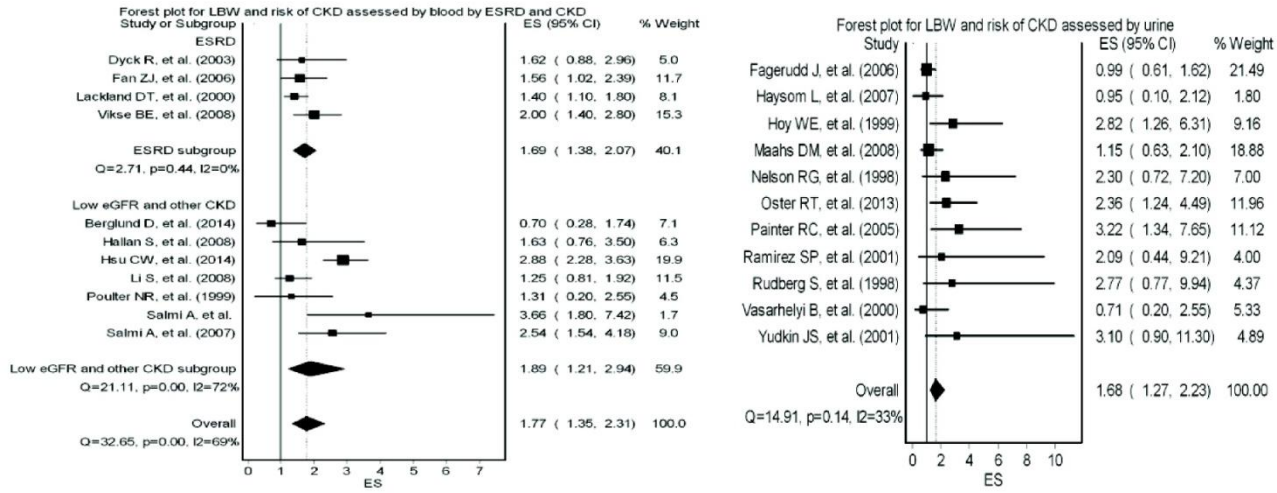
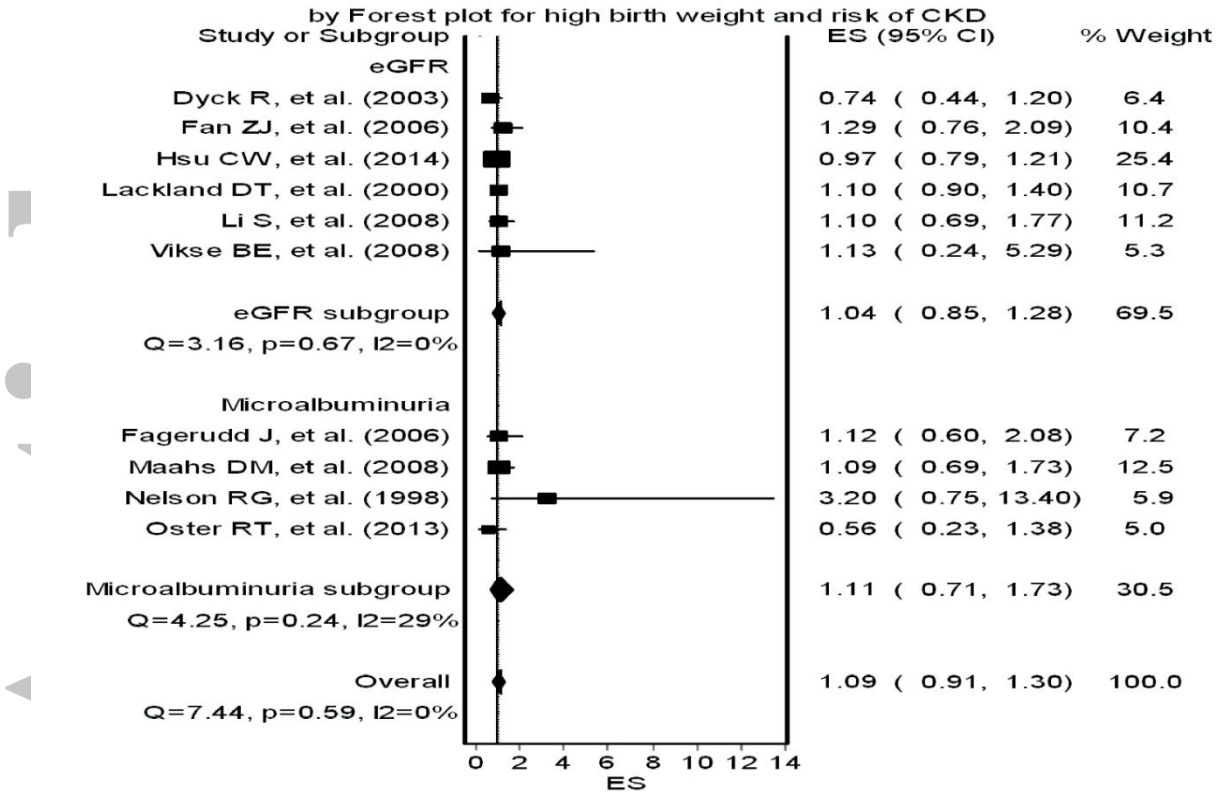


Figure 1: Selection framing of literature for systematic review and meta-analysis



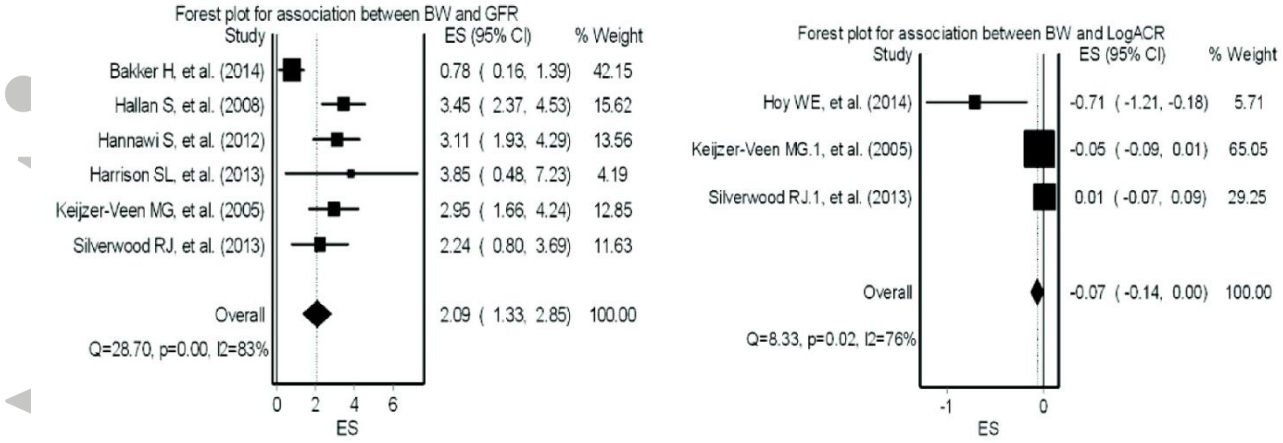
CKD: chronic kidney disease; LBW: Low birth weight; ESRD: End stage of renal disease (eGFR<15 ml/min/1.73 m^2

Figure 2: Meta-analysis of the risk of chronic renal disease among inborn with low birth weight assessed by blood and urine at adulthood



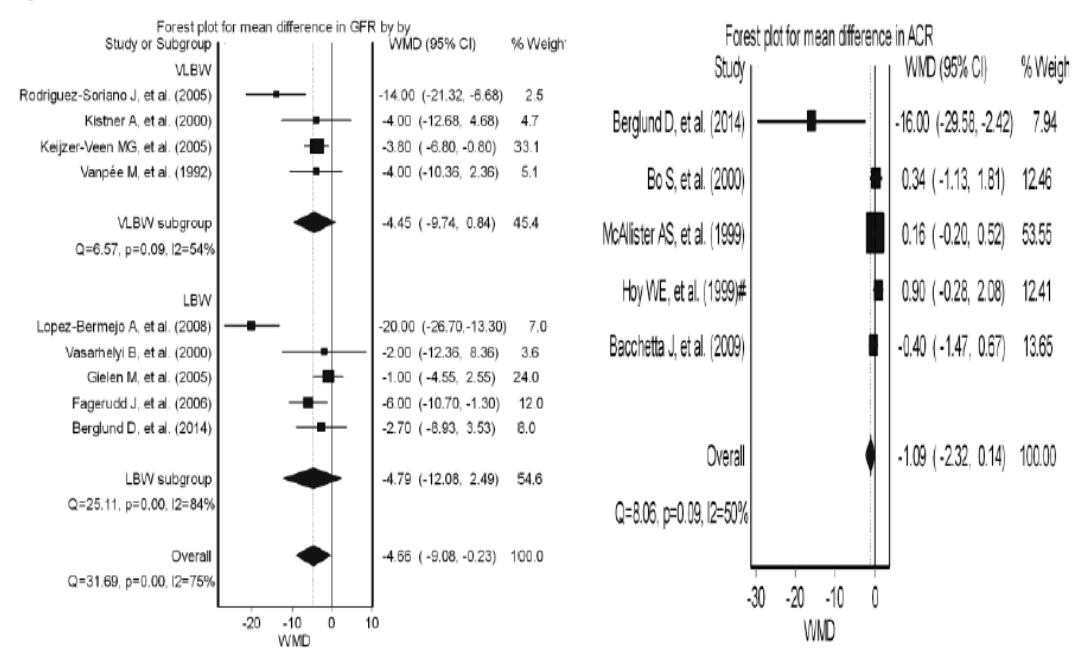
HBW: high birth weight; CKD: Chronic Kidney

Figure 3: Meta-analysis of the risk of chronic renal failure among inborn with high birth with at adulthood



BW: Birth weight; GFR: Glomerular filtration rate; ACR: Albumin creatinine ratio

Figure 4: Meta-analysis of the linear association between birth weight and glomerular filtration rate, and log transformed albumin creatinine ration



ACR: Albumin creatinine ration; GFR: Glomerular filtration rate; NBW: Normal birth weight; LBW: Low birth weight: WED: Weighted mean difference; VLBW: Very low birth weight

Figure 5: Meta-analysis of the difference of **glomerular filtration rate and albumin creatinine ration** between LBW and NBW people in adulthood

Table 1: Summary tables of studies measure Chronic Renal Disease and use effect size as Odds ratio/Beta-coefficient

	Study name	**Place**	**Study design**	**N**	**Age (year; mean±SD) and sex**	**Patient's character; birth weight (g) [mean±SD; range]**	**Specimen; Biomarker**	**Findings**	**Exposure (reference)**	**OR/β (95% CI)**	**Adjusted/Potential predictors**
1	Nelson RG, et al. (1998) [27]	United States	Chort study	308	34±6; both sex	Pima and closely-related Tohono O'odham Indians with Type 2 DM; [3382±575; 1619-5386]	Urine; Microalbuminuria: ACR≥30 mg/g	Significant U-shaped association between BW & microalbuminuria prevalence	BW<2,500 g (vs. 2,500-4,499 g)	2.3 (0.72, 7.2)	Age, sex, duration of DM, hemoglobin A1c, mean arterial BP
									HBW ≥4500 g	3.2 (0.75-13.4)	
2	Rudberg S, et al. (1998) [28]	Sweden	Nested case-control study, population-based cohort	214	Cases, 20.2±4.0; controls, 18.7±5.1; both sex	IDDM (controls matched for DM duration) [case:3573±583; control:3614±465]	Urine; Microalbuminuria: AER≥15 micg/min	No significant association between LBW and microalbuminuria prevalence	BW <2,500 g (v ≥2,500 gm)	2.77 (0.77, 9.94)	Unadjusted
3	Hoy WE,	Australi	Cross-	21	20-38	High-risk	Urine;	LBW associated with	BW <2,500	2.82 (1.26,	Age, sex, BMI,

	et al. (1999) [29]	a	sectional	7	(range); both sex	Aboriginal community; [2712±460; (1470-4080)]	Microalbuminuria: ACR≥300 mg/g	high rates of macroalbuminuria in high-risk community	g (v ≥2,500 g)	6.31)	SBP
4	Poulter NR, et al. (1999) [30]	United Kingdom	Retrospective cohort study	2602	45.5; female	Volunteers for registry of adult twins	eGFR<10th sex specific percentile (MDRD Study equation)	No association between LBW and eGFR among twin female (*unpublished analysis*)	BW <2,500 g (v 2,500-3,999 g)	1.31 (0.20, 2.55)	Age, sex, SES
5	Lackland DT, et al. (2000) [31]	USA	Case-control study	2690	34 (median); both sex	Cases had recent dialysis; Controls matched for age, sex, ethnicity; [black:3210; white:3361]	ESRD	LBW significantly contribute to early onset of ESRD	BW <2,500 g (v 3,000-3,499 g)	1.40 (1.1, 1.8)	Unadjusted
								HBW does not significantly contribute to early onset of ESRD	HBW ≥4000 g	1.1 (0.9, 1.4)	
6	Vasarhelyi B, et al. (2000) [32]	Hungary	Cohort study	126	18-22 (range); both sex	Healthy adolescents	Urine; Microalbuminuria: ACR≥30 mg/g	No association between LBW and kidney function observed	BW <2,500 g (v 2,500-3,999 g)	0.71 (0.20, 2.55)	Sex
7	Ramirez SP, et al.	Singap	Cross-	13	12; both	Children at 6th grade level or	Urine; Proteinuria:	Trend toward for LBW in children with	BW <2,500 g (v ≥2,500	2.09 (0.44,	Sex, ethnicity, prematurity,

	(2001) [33]	ore	sectional	26	sex	12-years under pilot national screening program; [3173±607]	≥1+ (≥30 mg/dL of protein) by dipstick	proteinuria	g)	9.21)	current weight, mean arterial BP
8	Yudkin JS, et al. (2001) [34]	United Kingdom	Cohort study	818	61.4±7.4; both sex	Born in Ware, Hertfordshire, Preston, Lancashire; [3402±561]	Urine; Microalbuminuria: AER>20 micg/min	Significant trend toward higher prevalence of microalbuminuria with lower ponderal index	Ponderal index in lower 3rd percentile (v highest 3rd)	3.10 (0.90, 11.30)	Age, sex, BMI, SBP, region, fasting glucose

Table 1: Summary tables of studies measure estimated Chronic Renal Disease and use effect size as Odds ratio/Beta-coefficient (continuation)

	Study name	Place	Study design	N	Age (year; mean±SD) and sex	Patient's character	Biomarker	Findings	Exposure (reference)	OR/β (95% CI)	Adjusted/Potential predictors
9	Dyck R, et al. (2003) [35]	Canada	Case-control study	878	Both sex	Indian & other Saskatchewan people; controls	ESRD	LBW significantly associated with ESRD in white female	BW <2,500 g (v 2,501-3,999 g)	1.62 (0.88, 2.96)	Unadjusted
								HBW did not associated with ESRD	HBW >4000 g	0.74 (0.44, 1.20)	
10	Keijzer-Veen MG, et al. (2005) [36]	The Netherlands	Cohort study	422	19.3±0.2; both sex	Born with a gestational age <32 wk.	GFR	Birth weight (SDs) was associated with GFR and Log ACR in young adults born very preterm		2.95 (1.66, 4.24)*	Sex
							LogACR			-0.05 (-0.09, -0.01)*	
11	Painter RC, et al. (2005) [37]	The Netherlands	Cohort study	724	48-53; both sex	Singletons born during Dutch famine (1944-1945); [3352±471]	Microalbuminuria: ACR≥2.5 g/mol	Exposure to famine mid gestation significantly associated with higher rates of offspring microalbuminuria at 50 years	Exposure to famine mid gestation (v non exposed)	3.22 (1.34, 7.65)	Age, sex, BMI, smoking, SES, SBP, IGT/NIDDM, cholesterol, ECG abnormalities
12	Fan ZJ, et al. (2006) [38]	United States	Cohort study	7505	18-50; ESRD, 33.9±0.1;	Medicaid beneficiaries (low income) with DM	ESRD	LBW significantly associated with ESRD, particularly in those with both DM &	BW <2,500 g (v 2,500-3,999 g)	1.56 (1.02, 2.39)	Age, sex, ethnicity, DM, hypertension

					normal; 37.6±0.6) ; both sex	&/or hypertension		hypertension			
								HBW was not associated with ESRD	HBW ≥4000 g	1.29 (0.79, 2.09)	
13	Fagerudd J, et al. (2006) [39]	Finland	Cohort study	1543	33±10; both sex	Type 1 DM with an age at onset <36 years, with insulin therapy initiated within 1 year after diagnosis	Diabetic nephropathy : AER> 200 micg/min, 300 mg/24 h; ACR >2.5/3.5 mg/mmol (M/F), or ESRD	No association between LBW and development of diabetic nephropathy	BW <10th percentile (v 50th-90th percentile)	0.99 (0.61, 1.62)	Gestational age
								No association between HBW and development of diabetic nephropathy	BW >90 percentile (v 50th-90th percentile)	1.12 (0.60, 2.08)	
14	Haysom L, et al. (2007) [40]	Australia	Cohort study	1382	8.81±2.02	Aboriginal & non-Aboriginal elementary school children	Microalbuminuria: ACR≥30 mg/g	No association between LBW and AEC (*unpublished analysis*)	BW <2,500 g (v 2,500-3,999 g)	0.95 (0.10, 2.12)	Age, sex, ethnicity, SES
15	Salmi A, et al. (2007) [41]	Australia	Cohort study	4502	≥25.0	Healthy adults	eGFR<10th sex specific percentile (Taylor equation)	LBW significantly associated with eGFR & 10thpercentile for sex	BW <2,500 g (v ≥2,500 g)	2.54 (1.54, 4.18)	Unadjusted

Table 1: Summary tables of studies measure estimated Chronic Renal Disease and use effect size as Odds ratio/Beta-coefficient (continuation)

	Study name	Place	Study design	N	Age (year; mean±SD) and sex	Patient's character	Biomarker	Findings	Exposure (reference)	OR/β (95% CI)	Adjusted/Potential predictors
16	Hallan S, et al. (2008) [42]	Norway	Cohort study	7457	20-30; VSGA: 24.2±2.8; SGA: 24.7±2.9; AGA: 24.7±2.9; both sex	VSGA: 2448±311; SGA:2851±253; AGA: 3499±411	eGFR<10th sex specific percentile (MDRD Study equation)	IUGR significantly associated with low-normal kidney function, effects less consistent in female	BW <3rd v 10th-90th percentile (2,450 v 2,870-4,190 g)	1.63 (0.76, 3.5) 3.45 (2.37, 4.53)*	Age, smoking, education, maternal factors (age, DM, kidney function, preeclampsia)
17	Maahs DM, et al. (2008) [43]	United States	Cohort study	3714	12.3; both sex	Youth younger than 20 years with	Urine; Microalbuminuria: AER>20 micg/min	LBW was not significantly associated with elevated ACR HBW was not significantly associated with elevated ACR	LBW<2500 g (v ≥2,500-4,000 g) HBW>4000 g	1.15 (0.63, 2.1) 1.09 (0.69, 1.73)	DM duration, age, sex, HbA1c%, gestational diabetic, ethnicity, DM type, BMI, SBP, DBP
18	Li S, et al. (2008) [44]	United States	Retrospective cohort study	1236 4	18-75; mean age: 49.1-13.5 both sex	Volunteers with DM, HTN, or family history of CKD, DM,	CKD: ACR 30 mg/g or eGFR<60 mL/min/1.73 m^2	LBW significantly associated with CKD only among male	BW <2,500 g (v 3,000-3,999 g) HBW	1.25 (0.81, 1.92) 1.10 (0.69,	Age, race, education, insurance, region, DM, HTN, CVD, family history of

						or HTN; 3195±781	(MDRD Study equation)		≥4000 g	1.77)	kidney disease, HTN control
19	Salmi A, et al. (2008) [45]	Australia	Case-control study	567	60.3±15; both sex	Cases were patient attended the Nephrology department. Controls were sex and closely matched age participated in AusDiab study; [case:3270±620; control:3460±590]	CKD stages 2-5: eGFR 60-90 mL/min/1.73 m^2 with proteinuria hematuria or eGFR<60 mL/min/1.73 m^2 (MDRD Study equation), or on dialysis therapy	LBW significantly more prevalent in patients with CKD compared with age- & sex-matched controls	BW <2,500 g (v 2,500-3,999 g)	3.60 (1.70, 7.60)	Age, sex, diabetes, hypertension, glomerulonephritis, and reno-vascular disease
20	Hannawi S, et al. (2012) [46]	Australia	Cohort study	1017	29-30	As like as Salmi A, et al. (2008)	eGFR (mL/min/1.73 m^2)	Birth weight was strongly associated with eGFR		3.17 (2.00, 4.35)*	
21	Vikse BE, et al.	Norway	Retrospective cohort	2.2 million	Age ESRD onset	Record linkage study of all	ESRD	LBW & BW for gestational age significantly associated	BW <2,500 g (v 2,500-4,499 g)	2.00 (1.4, 2.8)	Sex, birth year, birth order, congenital

	(2008) [47]		study	n	21.2±8.9; both sex	Norwegian children born 1967-2004		with risk of ESRD	HBW ≥4000 g	3.2 (0.75, 13.4)	malformation, multiple delivery, maternal factors (age, marital status, preeclampsia)

Table 1: Summary tables of studies measure estimated Chronic Renal Disease and use effect size as Odds ratio/Beta-coefficient (continuation)

	Study name	**Place**	**Study design**	**N**	**Age (year; mean±SD) and sex**	**Patient's character**	**Biomarker**	**Findings**	**Exposure (reference)**	**OR/β (95% CI)**	**Adjusted/Potential predictors**
22	Harrison SL, et al. (2013) [48]	United Kingdom	Cohort study	335	63-64; both sex	Cohort of the Newcastle Thousand Families study	eGFR (mL/min/1.73 m^2)	BW was significantly positively associated with eGFR.		3.85 (0.48, 7.23)*	Sex, smoking and BMI
23	Oster RT, et al. (2013) [49]	Canada	Cohort study	1439	32.1±17.2 (5-90); both sex	Canadian aboriginal	Dipstick-positive proteinuria and/or ACR>2.74 in females or >1.94 in males	LBW was significantly associated with proteinuria	LBW≤2500 g (v ≥2,500 g)	2.36 (1.24, 4.49)	Age and sex
								HBW was not associated with proteinuria	HBW≥4000 g	0.56 (0.23, 1.38)	
24	Silverwood RJ, et	United Kingdo	Cohort study	2198	62-64	Singleton children born	C (eGFRcys)	LBW was significantly associated with renal		2.24 (0.80, 3.69)*	Age, sex, self-reported diabetes

	al. (2013) [50]	m				in 1 week in March 1946 in England, Scotland, and Wales	LogACR	disease		0.010 (-0.065, 0.085)*	and midlife SBP trajectory, treatment of DM and HTN at 60–64, SBP at 60–64; overweight at 36
25	Bakker H, et al. (2014) [51]	Netherlands	Cohort study	6482	6; both sex	Generation R study	eGFR	Higher gestational age-adjusted birth weight was associated with higher eGFR		0.78 (0.16, 1.39)*	Gestational age
26	Berglund D, et al. (2014) [52]	United States	Cohort study	216	52.2± 9.6; both sex	Living donor nephrectomies	GFR using the plasma clearance of non-radioactive iohexol<60 mL/min/1.73 m^2	BW was not associated with GFR	LBW<2500 g	0.70 (0.28, 1.74)	Age, sex, BMI, time from donation, SBP, DBP
27	Hoy WE, et al. (2014) [53]	Australia	Retrospective Cohort study	655	15-39 (26.2)	Remote aboriginal people	LogACR	BW was associated log transformed ACR		-0.71 (-1.21, -0.18)*	Age, BMI at follow-up, a previous post streptococcal glomerulo-nephritis
2	Hsu CW, et al.	United	Case-control	2202	<1-35;	Cases were individuals	Diagnosed by ICD-9	LBW significantly	LBW<2500 g (v ≥2,500	2.88 (2.28,	Maternal DM,

8	(2014) [54]	States	study	6	both sex	with renal dysplasia/ aplasia and obstructive	codes [renal dysplasia/ aplasia 753.0/753.1	increased risk of CKD	g)	3.63)	BMI, and smoking
								HBW was not associated with risk of CKD	HBW≥4000 g	0.97 (0.79, 1.21)	Maternal BMI and smoking

Note: *effect size in beta coefficient otherwise odds ratio; ACR: albumin creatinine ratio; AER: albumin extrication rate; BMI: body mass index; BW: Birth weight; CKD: chronic renal disease; DM: diabetes mellitus; ELBW: extreme low birth weight; HBW: High birth weight; GFR: Glomerular filtration rate; eGRF: estimated GFR; LBW: low birth weight; IGT: impaired glucose tolerance test; IDDM: insulin dependent diabetes mellitus; MDRD: modified diet for renal disease; NIDDM: non-insulin dependent diabetes mellitus; SGA: Small for gestation; SPB: systolic blood pressure; DBP: diastolic blood pressure.

Table 2: Summary tables of studies measure mean difference of different biomarker for assessment of renal function

	Study name	Place	Study design	Age (year; mean ±SD) and sex)	Patient's character	Biomarker	Findings	Adjusted/Potential predictors	LBW			Control		
									N	BW	GFR	N	BW	GFR
1	Vanpée M, et al. (1992) [55]	Sweden	Cross-sectional study	8	18 months post-conceptual age infants	GFR	#Renal function markedly reduced during the neonatal period in very low birth weight infants		22	VLBW (GA 28.2± 1.5 weeks)	103± 12	25		107±10
2	Hoy WE, et al. (1999) [29]#	Australia	Cohort study	20-38	Adults aged over 20 years and above	ACR (Urine)	LBE contributes to renal disease compared to higher birth weight	Unadjusted	111	2220± 270	3.1±5 .64	206	2960± 330	2.2±4.03

3	McAllister AS, et al. (1999) [56]	Ireland	Cohort study	-	Healthy Caucasian volunteers, half low BW, half normal BW, all full term	ACR	No significant differences in mean serum creatinine, ACR. or AER between subjects with BW 2.500 v 3,000-4,000 g		12	28.0± 0.21	0.6±0 .58	12	27.9± 0.29	0.44± 0.24
4	Bo S, et al. (2000) [57]	Italy	Cohort study	33.7± 7.5	Twins without a familial history of diabetes and hypertension	ACR (Urine)	No significant correlation between BW & AER		36	2440± 610	3.19± 3.69	36	2719± 0.06	2.84± 2.59
5	Kistner A, et al. (2000) [58]	Sweden	Case-control study	26±1. 9	Women selected from hospital records & birth register, 15 preterm, 18 full-term SGA (BW 2,600 g), 17 full-term appropriate BW	GFR	No significant differences in GFR between preterm and full term with appropriate BW individuals	Unadjusted	15	1293± 283	103± 11	17	3720± 313	107±1 4
6	Vasarhelyi B, et al. (2000) [32]#	Hungary	Cohort study	20-22	Healthy adolescents	GFR	No association between LBW and kidney function observed	Sex	49		127± 22	16		125±1 7

7	Gielen M, et al. (2005) [59]	The Netherlands	Cohort study	25.6± 4.7	Monozygotic and dizygotic twins	GFR (24-hCC)	No significant difference in creatinine clearance between twins who both had LBW as compared with twins who both had a HBW	Unadjusted	304	2131± 270	93±34	349	2878± 314	94±22
8	Keijzer-Veen MG, et al. (2005) [36]#	The Netherlands	Cohort study	19.3± 0.2		GFR	GFR was significantly lower among SGA compared to AGA	Sex	215	1144± 259	105.1 ±16	207	1496± 317	108.9 ±15.4
9	Rodriguez-Soriano J, et al. (2005) [60]	Spain	Case-control study	6.1-12.4 (8.6)	School-age children. Case were born with BW<1000g; controls were health children of same age	GFR	GFR is significantly diminished in school-age children born with extreme prematurity	Unadjusted	40	540-100	117± 17	43	---	131±17

10	Fagerudd J, et al. (2006)[39]#	Finland	Cohort study	33±9	Percipients with a diagnosis of type 1 diabetes (E10 in ICD-10) attending the diabetic and renal out patient clinics and dialysis units	GFR (CC)	End-stage renal disease were equally prevalent in the various birth weight groups	---	154	2510±210†	90±26	622	2810±190†	69±29

Table 2: Summary tables of studies measure mean difference of different biomarker for assessment of renal function (continuation)

	Study name	Place	Study design	Age (year; mean ±SD) and sex)	Patient's character	Biomarker	Findings	Adjusted/Potential predictors	LBW			Control		
									N	BW	GFR	N	BW	GFR
11	Lopez-Bermejo A, et al. (2008) [61]	Spain	Cross-sectional study	9.5 ± 0.4; both sex	Healthy school-age children	GFR	Significant decrease in the eGFR was evident between lower and upper tertail of BW-SD score	Age, sex, GA, BMI		-2.0 to -0.7	101± 7.49		-0.1 to 1.6	121±14.99
12	Bacchetta J, et al. (2009) [62]	France	Cohort study	5.8-10.3 (7.6±1.3)	IUGR (BW<1000g and/or <32 wk GA); normotrophic (premature children with a BW above -2 SD and birth, and height at discharge above -2 SD for corresponding	ACR	Inborn with IUGR were at risk of decrease ACR during childhood	Unadjusted	23	IUGR	1.5±1.2	11	Normotrophic	1.9±1.6

					GA									
13	Berglund D, et al. (2014)[52]#	United States	Cohort study	41±10.3	Nephrectomies living donor free from diabetes, hypertension and have a GFR > 80 mL/min	GFR	Birth weight was not associated with GFR <60 ml/min/1.73m2, but was associated with albuminuria		15	---	69.6±11.9	201	----	72.3±11.6
						ACR (Blood)					4.0±26.7			20±10

Note: ACR: albumin creatinine ratio; AGA: Appropriate for gestational age; BMI: body mass index; BW: Birth weight; CC:Creatinine clearance GA: Gestational age; GFR: Glomerular filtration rate; LBW: low birth weight; SGA: Small for gestation; SPB: systolic blood pressure; DBP: diastolic blood pressure; VLBW: very low birth weight; †ponderal index (kg/m^3); #detail describe in Table 1;

Table 3: Summary of the studies not included in the meta-analysis

	Study name	**Place**	**Study design**	**N**	**Age (avg.)**	**Patient character**	**Method/Bio markers used**	**Findings**
1	Sandeman DD et al. (1992) [63]	United Kingdom	Cohort study	45	<40; both sex	Patient of T1DM	Microalbuminuria or proteinuria	Individuals with albuminuria/ proteinuria had significantly lower BW than those without nephropathy
2	Rossing P, et al. (1995) [64]	Denmark	Case-control	366	Cases, 41.0±9.3; controls, 42.1±9.8; both sex	Patients with IDDM with or without diabetic nephropathy	Diabetic nephropathy (persistent AER ≥300 mg/24 h)	Prevalence of diabetic nephropathy significantly higher in LBW women compared with high BW; no significant difference in men
3	Vestbo E, et al. (1996) [65]	Denmark	Cross-sectional study	620	48 (median)	Offspring of participants excluding subjects with DM or overt nephropathy	AER	No significant relationship between BW & AER
4	Yudkin JS, et al. (1997) [66]	United Kingdom	Cohort study	236	46-54; both sex	Study of participants born in & around Leningrad from January 1941-July 1942 before & during siege of Leningrad	AER	Consistent relationships of short stature with microalbuminuria and nephropathy in diabetic and non-diabetic individuals.
5	Erbey J, et al. (1997) [67]	United States	Cohort study	67	26.8; both sex	Patients with IDDM; mean duration of IDDM 18.1 years	Early onset albuminuria (AER ≥200 micg/min, onset at 21.8 y IDDM duration)	No association between LBW and shorter duration of IDDM at first presentation of albuminuria
6	Johnsen SP, et al.	Denmark	Nested study	545	40.7±5.6	Participants available birth	ACR	No significant associations between

	(2001) [68]		(population-based RCT)			records		BW, birth length, or ponderal index and ACR adjusted for age, BMI, smoking, alcohol consumption
7	Eshoj O, et al. (2002) [69]	Denmark	Case-control study	102	38 (median); both sex	Patient of T1DM	Diabetic nephropathy (AER ≥200 micg/min and/or ESRD)	No significant correlation between BW and AER or difference in prevalence of LBW between cases and controls
8	Iotova et al. (2002) [70]	Bulgaria	Case-control study	90	With MA, 20.9±2.6; no MA, 19.4±3.4	Adolescents with T1DM	Microalbuminuria	Subjects with microalbuminuria had significantly lower BW than controls
9	Laganovic et al. (2002) [71]	Croatia	Cohort study	72	38	Patients with mild form of essential hypertension	Microalbuminuria	No difference in albumin excretion between subjects with BW 3,250 g and others
10	Huxley RR, et al. (2004) [72]	United Kingdom	Cohort study	137	both sex	Offspring of pregnant mothers who participated in a wartime dietary survey	ACR	No significant relationship between BW and ACR adjusted for age, gender, BMI, parental social class and current social class
11	Iacobelli S, et al. (2007) [73]	France	Cohort study	96	7.2±0.6		Urine microlabumin	VLBW infants is not correlated with urine microlabumin
12	Kwinta P, et al. (2011) [74]	Poland	Cohort study	116	6.7; both sex	Case children born as ELBW infants; control born full-term	AER	No significant difference in AER between inborn with ELBW and full-term
13	Cassidy-Bushrow AE, et al.	United States	Cohort study	152	25±35 (30)	African and non-African American	LogGFR	BW is associated with renal function in African American

	(2012) [75]							children
14	Ichikawa T, et al. (2012) [76]	Japan	Cohort study	--	---	The numbers of LBW (<2,500 g) babies and ESRD need dialysis in 11 prefectures of Japan was included.	ESRD	The annual incidence of LBW was positively correlated with annual incidence of ESRD
15	Flynn JT, et al. (2014) [77]	United States	Cohort study	332	1-16 (12)	Children born with normal and abnormal weight [LBW (<2500 g), premature birth (<36 wk.), SGA (BW <10th percentile of GA)]	GFR	Abnormal birth history did not significant GFR in this cohort of children with CKD adjusted for age, sex and height

Table 4: Sensitivity analysis

Characters	Biomarker	
	Blood	**Urine**
LBW and CKD		
Geography		
USA and Canada	1.59 (1.15, 2.20)	1.64 (1.06, 2.55)
Europe	1.85 (1.36, 2.53)	1.56 (0.95, 2.55)
Asia and Australia	2.68 (1.73, 4.15)	2.28 (1.17, 4.43)
Age*		
≤30 years	2.30 (1.76, 3.00)	1.26 (0.79, 1.99)
31-50 years	1.57 (1.54, 4.18)	1.90 (1.28, 2.84)
≥51 years	3.66 (1.8, 7.42)	3.10 (0.90, 11.3)
Individual with Diabetic		
Diabetic	2.51 (1.99, 3.17)	1.38 (0.96, 1.99)
Non-diabetic	1.85 (1.41, 2.420	2.18 (1.46, 3.27)
Ethnic origin		
Aborigine	-	2.32 (1.43, 3.75)
Non-aborigine	-	1.50 (1.08, 2.09)
HBW and CKD (overall)		
Geography		
USA and Canada	1.10 (0.91, 1.32)	
Europe	1.12 (0.61, 2.06	

*Total 20 studies included in the analysis

#Only limited to studies used urine sue to none of the studies among aboriginal population used blood specimen