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Birth Weight Associated With Kidney Size in Middle-Aged Women

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The role of birth history, specifically birth weight, is a well-established risk factor for target organ diseases in adulthood. In 1989, Barker *et al.*[1] first presented an association between birth weight and cardiovascular disease among adults. Since that time, this finding has expanded to include kidney disease.[2] In a 2004 study, Hoy *et al.*[3] revealed that albuminuria in young adults was significantly and independently associated with a history of low birth weight (LBW). In their recently published follow-up study, Hoy *et al.*[4] found that estimated glomerular filtration rate was directly associated with birth weight and progressively worsening albuminuria over time among adults. A strong association between LBW and albuminuria was also observed among individuals with a history of poststreptococcal glomerulonephritis.[4] Furthermore, animal models and human kidney autopsy studies have revealed an association between LBW and low nephron number and abnormal nephron morphology result.[5]

As a precursor or potential predictor for development of overt kidney disease, the hypothesis of birth weight determining kidney size in adulthood has gained more interest in recent years as a proxy of nephron number. Intrauterine conditions, maternal health, and family history or genetic factors are factors found to affect birth weight and kidney size at birth. A recent study in Norway evaluated the effects of family history on birth weight and how the combination of family history of low birth and LBW in the subject increases risk of developing chronic kidney disease (CKD).[6] Individuals with LBW, with and without siblings with LBW, were found to have an increased risk of CKD compared with subjects with normal birth weight (NBW) (odds ratio 1.8 [1.56–2.08]).[6] Interestingly, Gjerde *et al.*[6] revealed that subjects with NBW who have siblings with LBW, who were small for gestational age, or who were preterm at birth had a 20% to 30% higher risk of CKD. When stratified by sex, males with LBW or who have siblings who were small for gestational age had higher risk of CKD than females.

In a previous study by Lillås *et al.*,[7] the authors revealed an association between history of LBW and reduced measured glomerular filtration rate (mGFR) among adults. Subjects with diabetes, on antihypertensive medications, with regular use of nonsteroidal anti-inflammatory drugs, with cancer, and with allergy to contrast were excluded as potential confounders. Overall, the mean mGFR was only slightly different between subjects with LBW and those with NBW ($P = 0.04$), and there was no difference in estimated glomerular filtration rate ($P = 0.8$). Nevertheless, when men and women were analyzed separately, significant differences were found among females born with LBW compared with females born with NBW ($P = 0.0006$). No difference in mGFR was observed among males born with LBW compared with males with NBW; thus, the authors concluded that the association between LBW and adulthood mGFR in women warranted further study.

Building on the observations made in their previous work, Lillås *et al.*[7] sought to evaluate for an association between birth weight and kidney size by magnetic resonance imaging (MRI) in middle adulthood and to determine if kidney volume mediates the difference in mGFR between healthy adults with LBW and those with NBW. Kidney function and kidney

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size, educational level, smoking status, and exercise frequency were compared among individuals with LBW (defined as ≤2300 kg) and NBW (3500–4000 kg). Kidney function and size were measured on 2 different days with Day 1 consisting of fasting blood samples, measurement of glomerular filtration rate by iohexol plasma clearance, blood pressure measurement, kidney ultrasound, and a questionnaire. Day 2, occurring at least 1 week after Day 1, took place in the afternoon and included an MRI (with and without contrast) of the kidneys to measure size.

Adults with a history of LBW had shorter stature at birth that persisted into adulthood and had higher blood pressure readings than adults with a history of NBW. NBW was associated with lower total kidney volume among females ($P = 0.0018$) but not males ($P = 0.69$). Statistical analysis revealed an association between mGFR and total kidney volume for the total group and when stratified by sex. There was no difference in education status, smoking status, or exercise habits between male and female and LBW and NBW.

The current work seeks to add to this complex and evolving body of research evaluating birth weight and long-term kidney outcomes and adds important points to the body of literature in this area. Similar to previous research, Lillås *et al.*[7] found that gestational age alone was not associated with kidney size. In addition to birth weight, other studies have revealed that weight for gestational age is a strong influence on kidney size in later life. As autopsy is the only method of accurately measuring nephron number, the need for a reliable and consistent method of measuring kidney volume and nephron number in patients is critical. Where we are currently unable to measure nephron number directly, kidney size is often used as a marker for nephron number. To date, kidney measurements obtained by MRI are the best estimation of nephron endowment that we currently have available. Furthermore, kidney volume obtained from MRI can serve as a surrogate marker for kidney disease. Despite the controversy surrounding the use of kidney size as a proxy for nephron number, renal autopsy studies reveal an association with kidney volume and CKD, and in this study, the authors revealed a positive relationship between kidney volume and mGFR.

To address the second aim of this study, the authors used a mediation analysis to evaluate the relationship between kidney volume and mGFR. The observed association between birth weight and mGFR and birth weight and kidney volume led authors to explore the relationship between kidney volume in mGFR. The authors found that both the direct and indirect effects of kidney volume on mGFR in the total group are significant. When stratified by sex, the observed effect in females remained quite strong, but there was no effect found in males. Thus, the observed effect of kidney volume on mGFR in the total group is a result of the strong relationship between these 2 variables in the female population.

Some limitations of the current work are the small sample size and lack of exploration into other factors known to affect kidney size. Previous works have pointed at natural decline in kidney size approximately on the fourth decade of life in women. On the basis of this model, we expect the females in this cohort to be in a state of declining kidney size, and potentially declining nephron endowment or efficiency regardless of birth weight or size. The authors briefly mention this known phenomenon, and exploration of the previous decade of life would add value to the argument of birth weight correlating with kidney size.

The authors propose an exploration of kidney volume and risk markers of cardiovascular disease; however, there is little discussion regarding exploration of this relationship. Identifying risk factors and biomarkers of cardiovascular disease, such as cholesterol, and evaluating a relationship with kidney volume would have strengthened the paper as few studies have explored the relationship between birth weight, kidney volume by MRI, and cardiovascular disease.

Previous studies of nephron number have been completed primarily in animal models and human autopsy studies. The clinical implications from this study involve the use of MRI to measure kidney volume, a more feasible *in vivo* surrogate measure for nephron number. This is something that could be used to predict future risk for kidney disease in persons at the highest risk for CKD, such as persons with a history of LBW. Perhaps MRI kidney volume assessment could be a diagnostic tool for targeting introduction of therapies which slow progression of CKD long term in the future.

In summary, the study by Lillås *et al.*[7] provide additional evidence for the association of birth weight with kidney size in adult women. Furthermore, the analysis used to reveal the effect of kidney volume on the interplay of birth weight and mGFR provides a potential mechanism for individuals with LBW who develop CKD in later life.

DISCLOSURE

All the authors declared no competing interests.

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