bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Relationship between birth weight and chronic kidney disease: an integrative analysis of observational studies and causal inference through genetic approaches

Xinghao Yu[1#], Zhongshang Yuan[2#], Haimiao Chen[1], Jiaji Yang[1], Yixin Gao[1], Fengjun Guan[3], Ping Zeng[1*], Shuiping Huang[1*]

[1] *Department of Epidemiology and Biostatistics, School of Public Health, Xuzhou Medical University, Xuzhou, Jiangsu, 221004, China*

[2] *Department of Biostatistics, School of Public Health, Shandong University, Jinan, Shandong, 250012, China*

[3] *Department of Pediatrics, Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221004, China*

[#]The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint first authors.

Correspondence to

zpstat@xzhmu.edu.cn

Ping Zeng

hsp@xzhmu.edu.cn

Shuiping Huang

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

ABSTRACT

Objective: Although many observational studies have shown that there was an inverse association between birth weight and chronic kidney disease (CKD) in adults, whether such association is causal remains largely unclear.

Methods: We first conducted a systematic review and meta-analysis to investigate the association between birth weight and CKD. Then using a set of valid instrumental variables for birth weight, we performed a two-sample Mendelian randomization (MR) to evaluate its causal effect on CKD based on summary association statistics available from large scale genome-wide association study (GWAS) (up to 143,677 individuals for birth weight and 118,147 individuals for CKD). We further validated the MR results with extensive sensitive analyses.

Results: The results of meta-analysis showed that individuals with low birth weight have about 76% (95% CI 36~126%) higher risk of CKD in late life compared with those with normal birth weight. Depending on 26 instrumental variables, the inverse variance weighted MR showed that the odds ratio per one SD increase of birth weight on CKD was estimated to be 0.91 (95% CI 0.72~1.14, p=0.396). The similar null association between birth weight and CKD is also observed using the weighted median method and maximum likelihood method as well as the Egger regression. Such non-significant association is robust against potential instrumental outliers and pleiotropic effects.

Conclusion: Our study identifies an inverse association between birth weight and adult CKD in observational studies, while it is not supportive of the causal role of birth weight on CKD based on our MR analysis.

Keywords: Birth weight; Chronic kidney disease; Mendelian randomization; Causal association; Genome wide association study

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

1. Introduction

Chronic kidney disease (CKD) is a common complex disease which influences both children and adult populations (Levey et al., 2015; Webster et al., 2017). At the initial disease stage, CKD is asymptomatic and may be ignored by sufferers. It is common that the diagnosis of CKD is made when disease symptoms already become severe. Moreover, a series of severe complications (e.g. renal failure, hypertension, cancer, infection and coronary heart disease) can occur with the decreased renal function of CKD patients (Di Lullo et al., 2015; Webster et al., 2017). Additionally, due to the decreased GFR during the disease progression as well as possible complications, the life quality of CKD patients is significantly lower than that of the general population.

It is estimated that the global prevalence of CKD ranges between 11% and 13%, and that CKD can account for 1.5% death worldwide, making it among the leading death risk and a global public health issue (Hill et al., 2016). World Health Organization (WHO) predicts that the deaths attributable to kidney-related diseases will increase by 31% (from ~871,000 in 2015 to ~1,143,000 in 2030) in the next decade due to the growing disease rate and aging population (Organization, 2018). Therefore, identifying the risk factors of CKD can promote our understanding of the pathogenesis of this disease, having the potential to ultimately lead to better prevention and treatment for CKD, and is also important in terms of the public health perspective (Luyckx and Brenner, 2015; Luyckx et al., 2017; Webster et al., 2017).

CKD has complicated etiologies and both genetic and non-genetic (e.g. lifestyle and environmental) risk factors to play an important role in the development of CKD (Jha et al., 2013; Webster et al., 2017; Iwagami et al., 2018; Wang et al., 2018). Some non-genetic risk factors (e.g. diabetes, hypertension, dyslipidemia and glomerulonephritis) were previously discovered in observational studies. Additionally, multiple genes (e.g. *NAT8*, *SLC7A9*, *UMOD*, *SHROOM3*, *GATM* and *MYH9*) were also identified to be associated with CKD and kidney-related traits (Chambers et al., 2010; Köttgen et al., 2010; Pattaro et al., 2016). More recently, several epidemiological studies have shown that CKD may originate from the life of the fetus —— a generalized hypothesis referred to as the fetal origins hypothesis first proposed by the British epidemiologist David Barker in 1990 (thus also known as Barker

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

hypothesis) (Barker, 1990; Luyckx and Brenner, 2015). The fetal origins hypothesis supposes that the risk for chronic non-communicable diseases (e.g. CKD and cardiovascular diseases) in later life can be partly attributed to the altered developmental programming and the long-term adverse adaptations to early undernutrition, both of which can lead to the structural and functional changes in multiple developing tissues and organs (Zeng et al., 2019b; Zeng and Zhou, 2019a). In the literature, birth weight is a widely used measurement for intrauterine environment; and low birth weight often serves as an indicator of impaired renal development in utero when investigating the influence of early growth on kidney-related outcomes. Although most previous studies (White et al., 2009; Luyckx and Brenner, 2015; Das et al., 2016), along with some animal experimental models (Barnett et al., 2017), illustrated that low birth weight was associated with an increased risk of CKD; owing to the heterogeneity in disease onset age, geographic diversity and ethnic differences, a few of other studies did not support the existence of the inverse relationship between birth weight and CKD (Fagerudd et al., 2006; Haysom et al., 2007), and sometimes even reported contradictory findings (Vasarhelyi et al., 2000). For example, no early glomerular and tubular damage was observed in young men with low birth weight compared with those with normal birth weight (Vasarhelyi et al., 2000).

The inconsistent observations regarding the relationship between birth weight and CKD may be also partly due to uncontrolled/unknown confounders which are commonly encountered in observational studies. Indeed, there are studies which suggested that the impaired kidney function in adulthood may be a consequence of high blood pressure (Vasarhelyi et al., 2000). Thus, it remains a concern when interpreting the observed relationship between birth weight and CKD as a causal association. A cohort longitudinal study may alleviate such concern and offer an important insight into the causal interpretation. However, longitudinal studies require large scale subjects and need very long-term follow-ups before CKD clinical presentation. Traditionally, randomized controlled trials (RCT) studies are the gold standard for inferring the causal effect of exposure on outcome. However, determining the causal relationship between birth weight and CKD by RCT is infeasible. It seems that the validation of the fetal origins hypothesis for CKD is extremely difficult in a traditional manner.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

In observational studies Mendelian randomization (MR) can help clarify the causal relationship between an exposure of interest and an outcome, and provide an efficient way for causal inference. Briefly, MR is a special instrumental variable method that employs genetic variants (e.g. single nucleotide polymorphisms (SNPs)) as instruments for an exposure (i.e. birth weight) and evaluates its causal effect on the outcome (i.e. CKD). In the past ten years the great success of genome-wide association studies (GWASs) makes it feasible to select suitable SNPs as effective instruments for causal inference in MR. In fact, MR has recently become a considerably popular approach of inferring causal relationship in observational research (Mokry et al., 2015; Zeng et al., 2019a; Zeng and Zhou, 2019b). Indeed, birth weight has been confirmed to be causally associated with many adult diseases (e.g. cardiovascular disease (Au Yeung et al., 2016; Zanetti et al., 2018) and type 2 diabetes (Wang et al., 2016)) through MR studies.

Motivated by those previous observations above, our main goal in this study was two aspects. First, to illuminate whether there exists an association between birth weight and CKD, we employed the systematic review and meta-analysis to provide a pooled conclusion. The result showed that birth weight is inversely associated with CKD, confirming the finding in other studies (Lackland et al., 2000; Fan et al., 2006; Al Salmi et al., 2008; Oster et al., 2013; Hirano et al., 2016). Furthermore, to determine whether this observed negative association is causal, we performed a largest and most comprehensive MR analysis based on summary statistic data available from large-scale GWASs with approximately 143,000 individuals for birth weight and ~118,000 individuals for CKD.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Materials and Methods

Systematic reviews and meta-analysis

Data sources and search strategies for previous studies

Following the guideline of preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher et al., 2009), we performed a literature search mainly on PubMed from January 1998 to April 2019 for articles on the relationship between birth weight (and related factors including premature birth and fetal development) and CKD. We made no restriction on study designs and considered both cohort and population-based studies; but we limited articles in English. Originally, a total of 2,072 articles (2,067 articles by searching and additional 5 articles by references scanning) were obtained (Fig. S1). The following exclusion criteria for articles filtering were employed: (1) the title and abstract did not contain any data on birth weight and/or CKD; (2) insufficient results were available on birth weight and CKD; (3) duplicated studies; (4) articles were a review, letter-to-editor, response or commentary article; and (5) articles were about clinical drug trials for CKD; (6) articles were about CKD in childhood. Based on those criteria, 20 studies were left in our final meta-analysis.

Data extraction and Statistical analysis in meta-analysis

For each article that was incorporated into our meta-analysis, two investigators (XH and PZ) independently carried out data extraction and quality assessment. From each article we extracted the information about study setting and design, population and sample size for case and control, effect size (e.g. odds ratio (OR), relative ratio (RR) or hazard ratio (HR)) as well as covariates that were adjusted for in the original analysis. The effect size heterogeneity among studies was tested by the Cochran's Q statistic (Thompson and Sharp, 1999). We estimated the combined effect of birth weight on CKD using a weighted meta-analysis method and evaluated the published bias by the Egger method and funnel plot (Egger et al., 1997). We also performed a leave-one-out (LOO) analysis to assess the influence of a single study.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

MR analysis

GWAS data sources for birth weight and CKD

In our meta-analysis above we found that there exists a robust inverse association between birth weight and CKD (see below for more details). To examine whether this identified association is causal, we further performed a MR analysis based on large scale GWAS genetic data of birth weight and CKD. To achieve this, we first yielded the genetic data of birth weight from the Early Growth Genetics (EGG) consortium (http://egg-consortium.org) (Horikoshi et al., 2016). In this study, birth weight was measured as a continuous variable and an additive linear regression was adopted for each SNP to detect its association with birth weight while controlling for available covariates (e.g. gestational age). After quality control of SNP genotypes and individuals, it contained summary association statistics (e.g. effect allele, marginal effect size, standard error, p value and sample size) for 16,245,523 genotyped and imputed SNPs on 143,677 individuals of European ancestry.

We next obtained the summary association statistics (e.g. marginal effect size, standard error and p value) of CKD from the CKDGen consortium (http://ckdgen.imbi.uni-freiburg.de/) (Pattaro et al., 2016). After quality control a total of 118,147 European individuals (12,385 cases and 105,762 controls) and 2,191,883 SNPs were available for this CKD GWAS. Besides CKD, we also attempted to explore the causal relationship between birth weight and other kidney-related phenotypes which included eGFR based on serum creatinine (eGFRcrea) and cystatin C (eGFRcys) (Pattaro et al., 2016), annual decline of eGFR (eGFR change) and rapid eGFR decline (Rapid Decline) (Gorski et al., 2015), urinary albumin-to-creatinine ratio (UACR) and microalbuminuria (MA) (Teumer et al., 2016). The used GWAS genetic data sets in our MR study are summarized in Table S1. Since participants had given informed consent for data sharing as described in each of the original GWASs and only summary association results were employed; therefore, ethical review was not needed for our study.

Estimation of causal effect of birth weight on CKD and sensitivity analyses

We then employed MR approaches to determine the causal relationship between birth weight and CKD. First, to ensure the validity of MR we carefully selected a set of independent index associated (p<5.00E-8) SNPs that can serve as valid instrumental

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

variables for birth weight. The summary information of those index SNPs for birth weight and CKD are shown in Table S2. Next, to quantitatively check whether the selected instruments for birth weight are strong, we calculated the proportion of phenotypic variance of birth weight explained by each instrument and computed the *F* statistic as an empirical indicator of strong/weak instrument (Noyce et al., 2017). We then performed the two-sample inverse-variance weighted (IVW) MR methods (Burgess et al., 2017) to estimate the causal effect of birth weight on CKD in terms of per standard deviation (SD) change in birth weight, where the SD of birth weight was estimated to be about 488 grams (Horikoshi et al., 2016). Before the causal effect estimation, to further ensure the validity of MR, we inspected the pleiotropic associations by removing instruments that may be potentially related to CKD with an adjusted p value less than 0.05 after Bonferroni correction. In our analysis no instruments were excluded by this conservative manner. To examine the robustness of results in the MR analysis, we carried out several sensitivity analyses: (1) weighted median-based method (Bowden et al., 2016) and maximum likelihood method (Burgess et al., 2013); (2) LOO analysis (Noyce et al., 2017) and MR-PRESSO test (Verbanck et al., 2018) to validate instrumental outliers that can substantially impact the causal effect estimate; (3) MR-Egger regression to detect directional pleiotropic effects of instrument variables (Burgess and Thompson, 2017).

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Result

Combined effect of birth weight on CKD in systematic review and meta-analysis

A total of 20 studies satisfied the inclusion criteria and were finally incorporated into our systematic review and meta-analysis (Fig. S1). Most of the included studies were carried out on European individuals. The extracted information of those studies is shown in Table 1. All the studies reported the risk of CKD for low birth weight compared with normal birth weight, and nine additionally reported the risk of CKD for high birth weight compared with normal birth weight. Note that the definition of low/high birth weight was slightly different across studies (see Table 1 for more details). Among those, 16 studies showed that low birth weight can increase the risk of CKD in later life. Additionally, five out of nine studies demonstrated that high birth weight can also raise the risk of CKD. Those results suggested that there may exist a U-shaped relationship between birth weight and CKD. We thus performed meta-analysis for the association between low or high birth weight with CKD separately (Fig. 1).

Owing to the presence of heterogeneous effect size of birth weight on CKD in those studies (the p values of the Q statistic are less than 0.05 for both low and high birth weight; Fig. 1), the results of the random-effects meta-analysis are displayed here. Specifically, we found that the risk of CKD for adult individuals with low birth weight is 76% (OR=1.76, 95% CI 1.37~2.26, p=1.27E-5) higher compared with those with normal birth weight (Fig. 1A), implying that lower birth weight leads to more vulnerable to CKD. This inverse relationship also holds in the sub-group meta-analyses in terms of gender or the type of study design (Fig. S2-S3). However, no significant association is observed between high birth weight and CKD (OR=1.05, 95% CI 0.81~1.37, p=0.713; Fig. 1B). These results are robust according to the LOO analyses which show that no single study can substantially dominate the final combined estimates (Table S3-S4). Additionally, the Egger test (p=0.170 for low birth weight and p=0.982 for high birth weight), together with the funnel plot (Fig. S2), demonstrates that the publication bias is less likely to influence the combined estimates in our meta-analysis. In summary, based on the results of meta-analysis above, we can conclude that an inverse association exists between birth weight and CKD, but no evidence is present for the observed U-shaped relationship.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Estimated causal effect of birth weight on CKD

In our MR analysis, a total of 26 independent index SNPs served as instrument variables for birth weight. They jointly explain a total of 0.91% of phenotypic variance for birth weight. The *F* statistics of those instruments range from 27.6 to 175.6 (with an average of 49.26), indicating that the weak instrument bias does not likely occur in our analysis. Little evidence of causal effect heterogeneity across instruments is observed (Q=23.08 and p=0.573); therefore, we employed the fixed-effects IVW MR method to estimate the causal effect and found that there exists a negative but non-significant casual association between birth weight and CKD. More specifically, the OR per one SD increase of birth weight on CKD is 0.91 (95% CI 0.72~1.14, p=0.396), consistent with those produced by the weighted median method (OR=0.86, 95% CI 0.62~1.18, p=0.346) and by the maximum likelihood approach (OR=0.91, 95% CI 0.72~1.14, p=0.414). The similarly null causal association was also observed if we employ other sets of instrumental variables for birth weight (Supplementary File). In addition, we also did not discover a significant casual association between birth weight and other kidney-related traits (Fig. S5).

We next examined whether there are potential instrument outliers and whether these outliers have a substantial influence on the estimate of causal effect. To do so, we created a scatter plot by drawing the effect sizes of SNPs of birth weight against those SNPs of CKD for all the used instruments (Fig. 2A). It is shown that no instrumental variables can be considered potential outliers. The result of MR-PRESSO also displays that there do not exist instrument outliers at the significance level of 0.05. Consistently, in terms of the result of the LOO analysis, no single instrument can have a substantial influence on the estimation of causal effect (Table S5). The OR per one SD increase of birth weight on CKD is estimated to be 0.55 (95% CI 0.26~1.17, p=0.120) using the MR-Egger regression. Furthermore, the MR-Egger regression removes the possibility of pleiotropic effects of instrument variables (the intercept=0.015, 95% CI -0.007~0.037, p=0.174). The funnel plot also presents a symmetric pattern around the causal effect point estimate (Fig. 2B), further indicating the absence of horizontal pleiotropy. Overall, the MR results do not provide statistically significant evidence that supports the direct causal association between birth weight and CKD.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Discussion

To understand the relationship between birth weight and CKD, in the present study we first performed a systematic review and meta-analysis. The results showed that individuals with low birth weight would have a higher risk of CKD in adulthood compared with those with normal weight, in line with previous observation (Poulter et al., 1999; Al Salmi et al., 2007; Khalsa et al., 2016). The mechanism underlying this inverse association between birth weight and CKD is very complicated (Di Lullo et al., 2015; Webster et al., 2017). Possible interpretations include the finding that low birth weight can lead to the reduction of the number of kidney nephrons (Luyckx et al., 2013). For example, it was observed that every 1 kg decrease of birth weight can result in about 250,000 reduction in the number of unilateral nephrons (Hoy et al., 2005). The relatively smaller number of nephrons for individuals with low birth weight implies a higher susceptibility to kidney diseases in later life (Brenner et al., 1988; Luyckx et al., 2017). This finding was also supported by animal models which showed that offspring had decreased kidney nephrons if being exposed to adverse environmental conditions during pregnancy (Bidani et al., 2013; Horowitz et al., 2015). However, our results provided little evidence supporting the existence of association between high birth weight and CKD although previous studies suggested high birth weight can also elevate the risk of CKD.

To investigate whether this observed negative association between birth weight and CKD in our meta-analysis is causal, we further carried out a two-sample MR analysis based on summary statistics publicly available from large scale GWASs. Because MR relies on the Mendel's second law which means that an allele of a gene can enter a gamete independently of another gene. Therefore, MR is less likely affected by confounding factors compared with observational studies (Burgess et al., 2017). In our MR analysis, to improve the statistical power and meet the model assumptions we used multiple instrument variables which were independent from each other and strongly associated with birth weight. We also tried to avoid the pleiotropic effects of instruments by removing index SNPs that may be potentially related with CKD. Further sensitive analyses (e.g. Egger regression) also excluded the likelihood of pleiotropy that can introduce bias into the causal effect estimation. However, the results of MR did not offer statistically significant evidence supporting the direct

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

causal relationship between birth weight and CKD.

Several explanations exist in this observed association. Especially, after birth the threat to the survival of the nephron still exists. Infants with low birth weight are often accompanied by a decrease in the number of nephrons due to impaired renal function development. The decrease in the number of nephrons may result in glomerular hypertrophy and high filtration rate, which ultimately leads to secondary glomerular sclerosis. As one of the important risk factors for CKD (Coca et al., 2012), acute kidney injury occurs in 18-40% of very low birth weight infants (Koralkar et al., 2011). Additionally, most of infants with very low birth weight receive at least one nephrotoxic drug treatment before discharge, which can potentially affect kidney function (Rhone et al., 2014). Infants with low birth weight or limited intrauterine growth often experience accelerated "catch-up" growth, which is also associated with CKD (Fagerberg et al., 2004).

Nevertheless, we note that the estimated causal effects between birth weight and CKD were consistent in the direction and magnitude through multiple MR methods (e.g. IVW, weighted median method and maximum likelihood estimation). There are several explanations for the failure of detecting a causal association between birth weight and CKD given the observation that low birth weight is robustly related to the increased risk of CKD in our meta-analysis. First, this inverse relationship in observational studies may be driven by shared genetic components between birth weight and CKD. To check this, we applied the linkage disequilibrium score regression (LDSC) (Bulik-Sullivan et al., 2015) to quantify the genetic covariance between birth weight and CKD. LDSC is a novel statistical genetic method for quantifying genetic correlation for two traits based on the genome-wide pleiotropy (note that our MR analysis has removed the influence of pleiotropic effects). With LDSC, we found a pronounced but nonsignificant genetic correlation between birth weight and CKD (R_g=-0.234, se=0.081, p=0.771; see Table S6 for more information), suggesting the common polygenic risk shared by low birth weight and CKD. More specifically, this means that some SNPs that are associated with low birth weight also related to the risk of CKD. Second, the failure of detecting non-zero causal effect of birth weight on CKD may be partly due to a lack of adequate statistical power. To examine this, we performed the statistical power calculation to discover an OR of 0.80

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

or 0.90 in the risk of CKD per unit change of birth weight following the approach shown in (Brion et al., 2013). Note that, these assumed ORs approximately equal to the estimated effect size of birth weight on CKD in our study. The results imply that we have a small to moderate power to detect the causal association between birth weight and CKD due to the small number of CKD cases (Fig. 3). For example, with the current sample size of CKD in our study (i.e. assume the sample size of adult CKD is 117,000 and the proportion of cases is 10.6%), the estimated statistical power is 17% or 25% to detect an OR of 0.80 or 0.90, respectively. Third, we cannot rule out the possibility that there exist some unknown pathways which mediate the influence of birth weight on CKD. Note that the existence of mediation effect (or indirect effect) of birth weight does not violate the model assumptions of MR. For example, it is well-established that low birth weight can increase the risk of coronary heart disease, diabetes and hypertension; the latter two are the major causes of CKD (Wingen et al., 1997; Jafar et al., 2003; Ardissino et al., 2004; Targher et al., 2008; Jha et al., 2013), implying that birth weight can have an impact on CKD by the metabolic or cardiovascular pathway.

Limitation

Finally, some limitations of this study should be considered. First, both birth weight (and all corresponding antecedents and early risk factors) and CKD are heterogeneous phenotypes; for example, among adult CKDs, polycystic kidney disease is currently known as a hereditary kidney disorder and is one of the most common autosomal dominant diseases (Gabow, 1993; Chapman et al., 2015). Diabetic nephropathy is caused by lifestyle and genetic factors and Hypertensive kidney disease is more caused by environmental factors(Go et al., 2004; Vivante and Hildebrandt, 2016). Therefore, when combining these heterogeneous CKDs together in analysis, a large degree of deviation may be introduced in our analysis. Second, as mentioned above, we have only a limited statistical power in our MR analysis due to the small sample size of cases in the CKD GWAS. Third, like many previous MR studies we hypothesized that there is a linear relationship between birth weight and CKD in our analysis. Linearity may be unreasonable in practice since previous epidemiological studies have found that high birth weight also increases the risk of CKD, implying a U-type relationship between birth weight and CKD. Therefore, we cannot completely remove the nonlinear influence of birth weight on CKD. Fourth, our MR relies on

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

summary statistics rather than individual-level data sets, thus we cannot analyze the relationship between very low/high birth weight and CKD due to lack of relevant data information, and we are also unable to conduct stratified analyses (e.g. in terms of gender; see Table 1) in our MR study.

In conclusion, our study identifies an inverse association between birth weight and CKD in observational studies, while it is not supportive of the causal role of birth weight on the risk of CKD based on our MR analysis.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Acknowledgements

We thank all the EGG and CKDGen consortium studies for making the summary data publicly available and we are grateful of all the investigators and participants contributed to those studies. The data analyses in the present study were supported by the high-performance computing at Xuzhou Medical University.

Author Contributions

PZ and SH conceived the idea for the study; PZ and XY obtained the data; PZ and XY cleared up the datasets; PZ, XY and ZY mainly performed the data analyses; HC, YG and JY helped clear and analyze the data; PZ, XY, ZY and FG interpreted the results of the data analyses; PZ and XY wrote the manuscript, and other authors approved the manuscript and provided relevant suggestions.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This study was supported by the National Natural Science Foundation of Jiangsu (BK20181472), Youth Foundation of Humanity and Social Science funded by Ministry of Education of China (18YJC910002), the China Postdoctoral Science Foundation (2018M630607 and 2019T120465), Jiangsu QingLan Research Project for Outstanding Young Teachers and Six Talent Peaks Project of Jiangsu Province of China (WSN-087), the Postdoctoral Science Foundation of Xuzhou Medical University, the National Natural Science Foundation of China (81402765), the Statistical Science Research Project from National Bureau of Statistics of China (2014LY112), the Postgraduate Research & Practice Innovation Program of Jiangsu Province (KYCX19_2250), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) for Xuzhou Medical University.

Supplementary material

Supplementary File.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Reference

1. Al Salmi, I., Hoy, W., Kondalsamy-Chennakesavan, S., Wang, Z., Gobe, G., Healy, H., et al. (2007). Adult chronic kidney disease patients have lower birth weight than the general Australian population. *Early Human Development* 83(Supp. 1)**,** S109-S109.
2. Al Salmi, I., Hoy, W.E., Kondalsamy-Chennakes, S., Wang, Z., Healy, H., and Shaw, J.E. (2008). Birth Weight and Stages of CKD: A Case-Control Study in an Australian Population. *American Journal of Kidney Diseases* 52(6)**,** 1070-1078. doi: 10.1053/j.ajkd.2008.04.028.
3. Ardissino, G., Testa, S., Dacco, V., Vigano, S., Taioli, E., Claris-Appiani, A., et al. (2004). Proteinuria as a predictor of disease progression in children with hypodysplastic nephropathy - Data from the ItalKid Project. *Pediatric Nephrology* 19(2)**,** 172-177. doi: 10.1007/s00467-003-1268-0.
4. Au Yeung, S.L., Lin, S.L., Li, A.M., and Schooling, C.M. (2016). Birth weight and risk of ischemic heart disease: A Mendelian randomization study. *Scientific Reports* 6**,** 38420. doi: 10.1038/srep38420.
5. Barker, D.J. (1990). The fetal and infant origins of adult disease. *British Medical Journal* 301(6761)**,** 1111-1111. doi: 10.1136/bmj.301.6761.1111.
6. Barnett, C., Nnoli, O., Abdulmahdi, W., Nesi, L., Shen, M., Zullo, J.A., et al. (2017). Low birth weight is associated with impaired murine kidney development and function. *Pediatr Res* 82(2)**,** 340-348. doi: 10.1038/pr.2017.53.
7. Berglund, D., MacDonald, D., Jackson, S., Spong, R., Issa, N., Kukla, A., et al. (2014). Low birthweight and risk of albuminuria in living kidney donors. *Clinical Transplantation* 28(3)**,** 361-367. doi: 10.1111/ctr.12321.
8. Bidani, A.K., Polichnowski, A.J., Loutzenhiser, R., and Griffin, K.A. (2013). Renal microvascular dysfunction, hypertension and CKD progression. *Current Opinion in Nephrology and Hypertension* 22(1)**,** 1-9. doi: 10.1097/MNH.0b013e32835b36c1.
9. Bowden, J., Smith, G.D., Haycock, P.C., and Burgess, S. (2016). Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genetic Epidemiology* 40(4)**,** 304-314. doi: 10.1002/gepi.21965.
10. Brenner, B.M., Garcia, D.L., and Anderson, S. (1988). Glomeruli and blood pressure. Less of one, more the other? *American journal of hypertension* 1(4 Pt 1)**,** 335-347. doi: 10.1093/ajh/1.4.335.
11. Brion, M.-J.A., Shakhbazov, K., and Visscher, P.M. (2013). Calculating statistical power in Mendelian randomization studies. *International Journal of Epidemiology* 42(5)**,** 1497-1501. doi: 10.1093/ije/dyt179.
12. Bulik-Sullivan, B.K., Loh, P.-R., Finucane, H.K., Ripke, S., Yang, J., Patterson, N., et al. (2015). LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics* 47(3)**,** 291. doi: 10.1038/ng.3211.
13. Burgess, S., Butterworth, A., and Thompson, S.G. (2013). Mendelian Randomization Analysis With Multiple Genetic Variants Using Summarized Data. *Genetic Epidemiology* 37(7)**,** 658-665. doi: 10.1002/gepi.21758.
14. Burgess, S., Small, D.S., and Thompson, S.G. (2017). A review of instrumental variable estimators for Mendelian randomization. *Statistical Methods in Medical Research* 26(5)**,** 2333-2355. doi: 10.1177/0962280215597579.
15. Burgess, S., and Thompson, S.G. (2017). Interpreting findings from Mendelian

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

randomization using the MR-Egger method. *European Journal of Epidemiology* 32(5), 377-389. doi: 10.1007/s10654-017-0255-x.

16. Chambers, J.C., Zhang, W., Lord, G.M., Van Der Harst, P., Lawlor, D.A., Sehmi, J.S., et al. (2010). Genetic loci influencing kidney function and chronic kidney disease. *Nature genetics* 42(5), 373. doi: 10.1038/ng.566.
17. Chapman, A.B., Devuyst, O., Eckardt, K.-U., Gansevoort, R.T., Harris, T., Horie, S., et al. (2015). Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney international* 88(1), 17-27. doi: 10.1038/ki.2015.59.
18. Coca, S.G., Singanamala, S., and Parikh, C.R. (2012). Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney international* 81(5), 442-448. doi: 10.1038/ki.2011.379.
19. Das, S.K., Mannan, M., Faruque, A.S.G., Ahmed, T., McIntyre, H.D., and Al Mamun, A. (2016). Effect of birth weight on adulthood renal function: A bias-adjusted meta-analytic approach. *Nephrology* 21(7), 547-565. doi: 10.1111/nep.12732.
20. Di Lullo, L., House, A., Gorini, A., Santoboni, A., Russo, D., and Ronco, C. (2015). Chronic kidney disease and cardiovascular complications. *Heart Failure Reviews* 20(3), 259-272. doi: 10.1007/s10741-014-9460-9.
21. Dyck, R., Klomp, H., Tan, L., and Stang, M.R. (2003). An association of maternal age and birth weight with end-stage renal disease in Saskatchewan - Sub-analysis of registered Indians and those with diabetes. *American Journal of Nephrology* 23(6), 395-402. doi: 10.1159/000074066.
22. Egger, M., Davey Smith, G., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *Bmj* 315(7109), 629-634. doi: 10.1136/bmj.315.7109.629.
23. Eriksson, J.G., Salonen, M.K., Kajantie, E., and Osmond, C. (2018). Prenatal Growth and CKD in Older Adults: Longitudinal Findings From the Helsinki Birth Cohort Study, 1924-1944. *Am J Kidney Dis* 71(1), 20-26. doi: 10.1053/j.ajkd.2017.06.030.
24. Fagerberg, B., Bondjers, L., and Nilsson, P. (2004). Low birth weight in combination with catch-up growth predicts the occurrence of the metabolic syndrome in men at late middle age: the Atherosclerosis and Insulin Resistance study. *J Intern Med* 256(3), 254-259. doi: 10.1111/j.1365-2796.2004.01361.x.
25. Fagerudd, J., Forsblom, C., Pettersson-Fernholm, K., Saraheimo, M., Wadén, J., Rönnback, M., et al. (2006). Low birth weight does not increase the risk of nephropathy in Finnish type 1 diabetic patients. *Nephrology Dialysis Transplantation* 21(8), 2159-2165.
26. Fan, Z.J., Lackland, D.T., Lipsitz, S.R., and Nicholas, J.S. (2006). The Association of Low Birthweight and Chronic Renal Failure among Medicaid Young Adults with Diabetes and/or Hypertension. *Public Health Reports* 121(3), 239-244. doi: 10.1177/003335490612100304.
27. Gabow, P.A. (1993). Autosomal dominant polycystic kidney disease. *New England Journal of Medicine* 329(5), 332-342. doi: 10.1056/NEJM199307293290508.
28. Go, A.S., Chertow, G.M., Fan, D., McCulloch, C.E., and Hsu, C.-y. (2004). Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *New England Journal of Medicine* 351(13), 1296-1305. doi: 10.1056/NEJMoa041031.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

29. Gorski, M., Tin, A., Garnaas, M., McMahon, G.M., Chu, A.Y., Tayo, B.O., et al. (2015). Genome-wide association study of kidney function decline in individuals of European descent. *Kidney International* 87(5)**,** 1017-1029. doi: 10.1038/ki.2014.361.
30. Hallan, S., Euser, A.M., Irgens, L.M., Finken, M.J., Holmen, J., and Dekker, F.W. (2008). Effect of intrauterine growth restriction on kidney function at young adult age: the Nord Trondelag Health (HUNT 2) Study. *Am J Kidney Dis* 51(1)**,** 10-20. doi: 10.1053/j.ajkd.2007.09.013.
31. Haysom, L., Williams, R., Hodson, E., Roy, L.P., Lyle, D., and Craig, J.C. (2007). Early chronic kidney disease in Aboriginal and non-Aboriginal Australian children: remoteness, socioeconomic disadvantage or race? *Kidney International* 71(8)**,** 787-794. doi: 10.1038/sj.ki.5002099.
32. Hill, N.R., Fatoba, S.T., Oke, J.L., Hirst, J.A., O'Callaghan, C.A., Lasserson, D.S., et al. (2016). Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *Plos One* 11(7). doi: 10.1371/journal.pone.0158765.
33. Hirano, D., Ishikura, K., Uemura, O., Ito, S., Wada, N., Hattori, M., et al. (2016). Association between low birth weight and childhood-onset chronic kidney disease in Japan: a combined analysis of a nationwide survey for paediatric chronic kidney disease and the National Vital Statistics Report. *Nephrol Dial Transplant* 31(11)**,** 1895-1900. doi: 10.1093/ndt/gfv425.
34. Horikoshi, M., Beaumont, R.N., Day, F.R., Warrington, N.M., Kooijman, M.N., Fernandez-Tajes, J., et al. (2016). Genome-wide associations for birth weight and correlations with adult disease. *Nature* 538(7624)**,** 248. doi: 10.1038/nature19806.
35. Horowitz, B., Miskulin, D., and Zager, P. (2015). Epidemiology of Hypertension in CKD. *Advances in Chronic Kidney Disease* 22(2)**,** 88-95. doi: 10.1053/j.ackd.2014.09.004.
36. Hoy, W.E., Hughson, M.D., Bertram, J.F., Douglas-Denton, R., and Amann, K. (2005). Nephron number, hypertension, renal disease, and renal failure. *Journal of the American Society of Nephrology* 16(9)**,** 2557-2564. doi: 10.1681/asn.2005020172.
37. Iwagami, M., Mansfield, K.E., Hayes, J.F., Walters, K., Osborn, D.P.J., Smeeth, L., et al. (2018). Severe mental illness and chronic kidney disease: a cross-sectional study in the United Kingdom. *Clinical Epidemiology* 10. doi: 10.2147/clep.s154841.
38. Jafar, T.H., Stark, P.C., Schmid, C.H., Landa, M., Maschio, G., de Jong, P.E., et al. (2003). Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition - A patient-level meta-analysis. *Annals of Internal Medicine* 139(4)**,** 244-252. doi: 10.7326/0003-4819-139-4-200308190-00006.
39. Jha, V., Garcia-Garcia, G., Iseki, K., Li, Z., Naicker, S., Plattner, B., et al. (2013). Chronic kidney disease: global dimension and perspectives. *Lancet* 382(9888)**,** 260-272. doi: 10.1016/s0140-6736(13)60687-x.
40. Khalsa, D.D.K., Beydoun, H.A., and Carmody, J.B. (2016). Prevalence of chronic kidney disease risk factors among low birth weight adolescents. *Pediatric Nephrology* 31(9)**,** 1509-1516. doi: 10.1007/s00467-016-3384-7.
41. Koralkar, R., Ambalavanan, N., Levitan, E.B., McGwin, G., Goldstein, S., and Askenazi, D. (2011). Acute kidney injury reduces survival in very low birth weight infants. *Pediatric research* 69(4)**,** 354. doi: 10.1203/PDR.0b013e31820b95ca.
42. Köttgen, A., Pattaro, C., Böger, C.A., Fuchsberger, C., Olden, M., Glazer, N.L., et

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

559 al. (2010). New loci associated with kidney function and chronic kidney disease.
560 *Nature genetics* 42(5)**,** 376. doi: 10.1038/ng.568.
561 43. Lackland, D.T., Bendall, H.E., Osmond, C., Egan, B.M., and Barker, D.J. (2000).
562 Low birth weights contribute to high rates of early-onset chronic renal failure in
563 the Southeastern United States. *Arch Intern Med* 160(10)**,** 1472-1476.
564 44. Lackland, D.T., Egan, B.M., Fan, Z.J., and Syddall, H.E. (2001). Low birth
565 weight contributes to the excess prevalence of end-stage renal disease in African
566 Americans. *J Clin Hypertens (Greenwich)* 3(1)**,** 29-31. doi:
567 10.1111/j.1524-6175.2001.00828.x.
568 45. Levey, A.S., Becker, C., and Inker, L.A. (2015). Glomerular Filtration Rate and
569 Albuminuria for Detection and Staging of Acute and Chronic Kidney Disease in
570 Adults A Systematic Review. *Jama-Journal of the American Medical Association*
571 313(8)**,** 837-846. doi: 10.1001/jama.2015.0602.
572 46. Li, S., Chen, S.C., Shlipak, M., Bakris, G., McCullough, P.A., Sowers, J., et al.
573 (2008). Low birth weight is associated with chronic kidney disease only in men.
574 *Kidney Int* 73(5)**,** 637-642. doi: 10.1038/sj.ki.5002747.
575 47. Luyckx, V.A., Bertram, J.F., Brenner, B.M., Fall, C., Hoy, W.E., Ozanne, S.E., et
576 al. (2013). Effect of fetal and child health on kidney development and long-term
577 risk of hypertension and kidney disease. *Lancet* 382(9888)**,** 273-283. doi:
578 10.1016/s0140-6736(13)60311-6.
579 48. Luyckx, V.A., and Brenner, B.M. (2015). Birth weight, malnutrition and
580 kidney-associated outcomes-a global concern. *Nature Reviews Nephrology* 11(3)**,**
581 135-149. doi: 10.1038/nrneph.2014.251.
582 49. Luyckx, V.A., Perico, N., Somaschini, M., Manfellotto, D., Valensise, H., Cetin, I.,
583 et al. (2017). A developmental approach to the prevention of hypertension and
584 kidney disease: a report from the Low Birth Weight and Nephron Number
585 Working Group. *Lancet* 390(10092)**,** 424-428. doi:
586 10.1016/s0140-6736(17)30576-7.
587 50. Moher, D., Liberati, A., Tetzlaff, J., and Altman, D.G. (2009). Preferred reporting
588 items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*
589 *(Clinical Research Ed.)* 339. doi: 10.1136/bmj.b2535.
590 51. Mokry, L.E., Ross, S., Ahmad, O.S., Forgetta, V., Smith, G.D., Leong, A., et al.
591 (2015). Vitamin D and Risk of Multiple Sclerosis: A Mendelian Randomization
592 Study. *Plos Medicine* 12(8). doi: 10.1371/journal.pmed.1001866.
593 52. Nelson, R.G., Morgenstern, H., and Bennett, P.H. (1998). Birth weight and renal
594 disease in Pima Indians with type 2 diabetes mellitus. *Am J Epidemiol* 148(7)**,**
595 650-656. doi: 10.1093/aje/148.7.650.
596 53. Noyce, A.J., Kia, D.A., Hemani, G., Nicolas, A., Price, T.R., De Pablo-Fernandez,
597 E., et al. (2017). Estimating the causal influence of body mass index on risk of
598 Parkinson disease: A Mendelian randomisation study. *Plos Medicine* 14(6). doi:
599 10.1371/journal.pmed.1002314.
600 54. Organization, W.H. (2018). "Mortality and global health estimates: Causes of
601 death; Projections for 2015–2030; Projection of death rates". Geneva: WHO).
602 55. Oster, R.T., Luyckx, V.A., and Toth, E.L. (2013). Birth weight predicts both
603 proteinuria and overweight/obesity in a rural population of Aboriginal and
604 non-Aboriginal Canadians. *Journal of Developmental Origins of Health and*
605 *Disease* 4(2)**,** 139-145. doi: 10.1017/s2040174412000724.
606 56. Painter, R.C., Roseboom, T.J., Van Montfrans, G.A., Bossuyt, P.M., Krediet, R.T.,
607 Osmond, C., et al. (2005). Microalbuminuria in adults after prenatal exposure to
608 the Dutch famine. *Journal of the American Society of Nephrology* 16(1)**,** 189-194.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

609 doi: 10.1681/ASN.2004060474.
610 57. Pattaro, C., Teumer, A., Gorski, M., Chu, A.Y., Li, M., Mijatovic, V., et al. (2016).
611 Genetic associations at 53 loci highlight cell types and biological pathways
612 relevant for kidney function. *Nature Communications* 7. doi:
613 10.1038/ncomms10023.
614 58. Poulter, N.R., Chang, C.L., MacGregor, A.J., Snieder, H., and Spector, T.D.
615 (1999). Association between birthweight and adult blood pressure in twins:
616 historical cohort study. *British Medical Journal* 319(7221)**,** 1330-1333. doi:
617 10.1136/bmj.319.7221.1330.
618 59. Rhone, E.T., Carmody, J.B., Swanson, J.R., and Charlton, J.R. (2014).
619 Nephrotoxic medication exposure in very low birth weight infants. *The Journal of*
620 *Maternal-Fetal & Neonatal Medicine* 27(14)**,** 1485-1490. doi:
621 10.3109/14767058.2013.860522.
622 60. Ruggajo, P., Svarstad, E., Leh, S., Marti, H.P., Reisaether, A.V., and Vikse, B.E.
623 (2016). Low Birth Weight and Risk of Progression to End Stage Renal Disease in
624 IgA Nephropathy--A Retrospective Registry-Based Cohort Study. *PLoS One*
625 11(4)**,** e0153819. doi: 10.1371/journal.pone.0153819.
626 61. Targher, G., Chonchol, M., Bertolini, L., Rodella, S., Zenari, L., Lippi, G., et al.
627 (2008). Increased Risk of CKD among Type 2 Diabetics with Nonalcoholic Fatty
628 Liver Disease. *Journal of the American Society of Nephrology* 19(8)**,** 1564-1570.
629 doi: 10.1681/asn.2007101155.
630 62. Teumer, A., Tin, A., Sorice, R., Gorski, M., Yeo, N.C., Chu, A.Y., et al. (2016).
631 Genome-wide Association Studies Identify Genetic Loci Associated With
632 Albuminuria in Diabetes. *Diabetes* 65(3)**,** 803-817. doi: 10.2337/db15-1313.
633 63. Thompson, S.G., and Sharp, S.J. (1999). Explaining heterogeneity in
634 meta-analysis: A comparison of methods. *Statistics in Medicine* 18(20)**,**
635 2693-2708. doi:
636 10.1002/(sici)1097-0258(19991030)18:20<2693::aid-sim235>3.0.co;2-v.
637 64. Vasarhelyi, B., Dobos, M., Reusz, G.S., Szabo, A., and Tulassay, T. (2000).
638 Normal kidney function and elevated natriuresis in young men born with low
639 birth weight. *Pediatr Nephrol* 15(1-2)**,** 96-100.
640 65. Verbanck, M., Chen, C.-Y., Neale, B., and Do, R. (2018). Detection of
641 widespread horizontal pleiotropy in causal relationships inferred from Mendelian
642 randomization between complex traits and diseases. *Nature Genetics* 50(5)**,** 693.
643 doi: 10.1038/s41588-018-0099-7.
644 66. Vikse, B.E., Irgens, L.M., Leivestad, T., Hallan, S., and Iversen, B.M. (2008).
645 Low birth weight increases risk for end-stage renal disease. *J Am Soc Nephrol*
646 19(1)**,** 151-157. doi: 10.1681/asn.2007020252.
647 67. Vivante, A., and Hildebrandt, F. (2016). Exploring the genetic basis of early-onset
648 chronic kidney disease. *Nature Reviews Nephrology* 12(3)**,** 133. doi:
649 10.1038/nrneph.2015.205.
650 68. Wang, J., Wang, B., Liang, M., Wang, G., Li, J., Zhang, Y., et al. (2018).
651 Independent and combined effect of bilirubin and smoking on the progression of
652 chronic kidney disease. *Clinical Epidemiology* 10**,** 121-132. doi:
653 10.2147/clep.s150687.
654 69. Wang, T., Huang, T., Li, Y., Zheng, Y., Manson, J.E., Hu, F.B., et al. (2016). Low
655 birthweight and risk of type 2 diabetes: a Mendelian randomisation study.
656 *Diabetologia* 59(9)**,** 1920-1927. doi: 10.1007/s00125-016-4019-z.
657 70. Webster, A.C., Nagler, E.V., Morton, R.L., and Masson, P. (2017). Chronic kidney
658 disease. *Lancet* 389(10075)**,** 1238-1252. doi: 10.1016/s0140-6736(16)32064-5.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

71. White, S.L., Perkovic, V., Cass, A., Chang, C.L., Poulter, N.R., Spector, T., et al. (2009). Is Low Birth Weight an Antecedent of CKD in Later Life? A Systematic Review of Observational Studies. *American Journal of Kidney Diseases* 54(2)**,** 248-261. doi: 10.1053/j.ajkd.2008.12.042.
72. Wingen, A.M., FabianBach, C., Schaefer, F., and Mehls, O. (1997). Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. *Lancet* 349(9059)**,** 1117-1123. doi: 10.1016/s0140-6736(96)09260-4.
73. Yudkin, J.S., Martyn, C.N., Phillips, D.I.W., and Gale, C.R. (2001). Associations of micro-albuminuria with intra-uterine growth retardation. *Nephron* 89(3)**,** 309-314. doi: 10.1159/000046091.
74. Zanetti, D., Tikkanen, E., Gustafsson, S., Priest, J.R., Burgess, S., and Ingelsson, E. (2018). Birthweight, Type 2 Diabetes Mellitus, and Cardiovascular Disease Addressing the Barker Hypothesis With Mendelian Randomization. *Circulation-Genomic and Precision Medicine* 11(6). doi: 10.1161/circgen.117.002054.
75. Zeng, P., Yu, X., and Xu, H. (2019). Association between premorbid body mass index and amyotrophic lateral sclerosis: causal inference through genetic approaches. *Frontiers in Neurology (in presss)*. doi: 10.1101/526186.
76. Zeng, P., Yu, X., and Zhou, X. (2019). Birth weight is not causally associated with adult asthma: results from instrumental variable analyses. *Scientific Reports* 9(1)**,** 7647. doi: 10.1038/s41598-019-44114-5.
77. Zeng, P., and Zhou, X. (2019). Causal Association between Birth Weight and Adult Diseases: Evidence from a Mendelian Randomisation Analysis. *Frontiers in Genetics* 10**,** 618. doi: 10.3389/fgene.2019.00618.
78. Zeng, P., and Zhou, X. (2019). Causal effects of blood lipids on amyotrophic lateral sclerosis: a Mendelian randomization study. *Human molecular genetics* 28(4)**,** 688-697. doi: 10.1093/hmg/ddy384.

Table and Figure Legend

Table 1. Summary information of 20 studies included in the meta-analysis for investigating the relationship between birth weight and chronic kidney disease

First author (year)	Country	Study design	*N*	Exposure vs Reference (g)	OR (95% CI)	Covariates
Information for the relationship between low birth weight and CKD						
Nelson (1998) (Nelson et al., 1998)	USA	cohort study	308	<2,500 vs 2,500~4,499	2.30 (0.72~7.00)	age, sex, duration of DM, hemoglobin, A1c, mean arterial BP
Lackland (2000) (Lackland et al., 2000)	USA	case-control	3,690	<2,500 vs 3,000~3,499	1.40 (1.10~1.80)	unadjusted
Vasarhelyi (2000) (Vasarhelyi et al., 2000)	Hungary	cohort study	126	<2,500 vs 3,000~3,999	0.71 (0.20~2.80)	Sex
Lackland (2001) (Lackland et al., 2001)	USA	case-control	1,230	<2,500 vs 3,000~3,499	1.70 (1.00~2.80)	unadjusted
Yudkin (2001) (Yudkin et al., 2001)	UK	cohort study	818	ponderal index in lower 3rd vs other	3.10 (0.90~11.30)	age, sex, BMI, SBP, region, fasting glucose
Dyck (2003) (Dyck et al., 2003)	Canada	case-control	878	<2,500 vs 2,501~3,999	1.62 (0.88~2.96)	unadjusted
Painter (2005) (Painter et al., 2005)	Netherlands	cohort study	724	exposure to famine mid-gestation vs. non-exposed	3.22 (1.34~7.65)	age, sex, BMI, smoking, SES, SBP, IGT/NIDDM, cholesterol, ECG abnormalities
Fagerudd (2006) (Fagerudd et al., 2006)	Finland	cohort study	1,543	<10th percentile vs 50 to 90th percentile	0.99 (0.61, 1.62)	gestational age
Fan (2006) (Fan et al., 2006)	USA	cohort study	7,505	<2,500 vs 2,500~3,999	1.56 (1.02~2.39)	age, sex, ethnicity, DM, hypertension
Salmi (2007) (Al Salmi et al., 2007)	Australia	cohort study	4,502	<2,500 vs ≥2,500	2.54 (1.54~4.18)	unadjusted
Haysom (2007) (Haysom et al., 2007)	Australia	cohort study	1,382	<2,500 vs 2,500~3,999	0.95 (0.10~2.12)	age, sex, ethnicity, SES
Salmi (2008) (Al Salmi et al., 2008)	Australia	cross-control	567	<2,500 vs 3,000~3,999	3.60 (1.70~7.60)	age, sex, diabetes, hypertension, glomerulonephritis, and Reno-vascular disease
Hallan (2008) (Hallan et al., 2008)	Norway	cohort study	7,457	<3rd vs 10th-90th percentile	1.63 (0.76~3.50)	age, smoking, education, maternal factors
Li (2008) (Li et al., 2008)	USA	retrospective cohort	12,364	<2,500 vs 3,000~3,999	1.25 (0.81~1.92)	age, race, education, insurance, region, DM, HTN, CVD, family history of kidney disease, HTN control
Vikse (2008) (Vikse et al., 2008)	Norway	retrospective cohort	2.2 million	<2,500 vs 2,500~4,499	2.00 (1.40~2.80)	sex, birth year, birth order, congenital malformation, multiple delivery, maternal factors (age, marital status, preeclampsia)
Oster (2013) (Oster et al., 2013)	Canada	cohort study	1,439	<2,500 vs ≥2,500	2.36 (1.24~4.49)	age and sex
Berglund (2014) (Berglund et al., 2014)	USA	case-control	216	< 2500	0.70 (0.28~1.74)	age, sex, BMI, time from donation, SBP, DBP

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Hirano (2016) (Hirano et al., 2016)	Japan	case-control	20,620,003	<2,500 vs ≥2,500	4.21 (3.37~5.26)	birth year
Ruggajo (2016) (Ruggajo et al., 2016)	Norway	retrospective cohort	471	<10th percentile vs >10th percentile	1.40 (0.69~2.70)	glomerular filtration
Eriksson (2018) (Eriksson et al., 2018)	Finland	cohort study	1,060	≤2,500 vs 3,000-3,499	1.32 (0.79~2.22)	unadjusted
Information for the relationship between high birth weight and CKD						
Nelson (1998) (Nelson et al., 1998)	USA	cohort study	308	≥4,500 vs 2,500~4,499	3.20 (0.75~13.40)	age, sex, duration of DM, hemoglobin, A1c, mean arterial BP
Lackland (2000) (Lackland et al., 2000)	USA	case-control	2,690	≥4,000 vs 3,000~3,499	1.10 (0.90~1.40)	unadjusted
Dyck (2003) (Dyck et al., 2003)	Canada	case-control	878	>4,000 vs 2,501~3,999	0.74 (0.44~1.20)	unadjusted
Fagerudd (2006) (Fagerudd et al., 2006)	Finland	cohort study	1,543	>90th percentile vs 50 to 90th percentile	1.12 (0.60~2.08)	gestational age
Fan (2006) (Fan et al., 2006)	USA	cohort study	7,505	≥4,000 vs 2,500~3,999	1.29 (0.79~2.09)	age, sex, ethnicity, DM, hypertension
Li (2008) (Li et al., 2008)	USA	retrospective cohort	12,364	≥4,000 vs 3,000~3,999	1.41 (1.06~1.88)	age, race, education, insurance, region, DM, HTN, CVD, family history of kidney disease, HTN control
Vikse (2008) (Vikse et al., 2008)	Norway	retrospective cohort	2.2M	≥4,000 vs 2,501~4,499	3.20 (0.75~13.40)	sex, birth year, birth order, congenital malformation, multiple delivery, maternal factors (age, marital status, preeclampsia)
Oster (2013) (Oster et al., 2013)	Canada	cohort study	1,439	≥4,000 vs ≥2,500	0.56 (0.23~1.38)	age and sex
Eriksson (2018) (Eriksson et al., 2018)	Finland	cohort study	20,431	≥4,000 vs 3,000-3,499	0.59 (0.39~1.00)	unadjusted
Information for the relationship between low birth weight and CKD for male						
Lackland (2000) (Lackland et al., 2000)	USA	case-control	2,676	<2,500 vs 3,000~3,499	1.20 (0.90~1.60)	unadjusted
Dyck (2003) (Dyck et al., 2003)	Canada	case-control	183	<2,500 vs 2,501~3,999	1.12 (0.50~2.52)	unadjusted
Salmi (2007) (Al Salmi et al., 2007)	Australia	cohort study	NA	<2,500 vs ≥2,500	3.40 (2.11~5.36)	unadjusted
Hallan (2008) (Hallan et al., 2008)	Norway	cohort study	3,534	<2,450 vs 2,870-4,190	2.68 (1.58~4.51)	age, smoking, education, maternal factors
Li (2008) (Li et al., 2008)	USA	retrospective cohort	2,920	<2,500 vs 3,000~3,999	1.65 (0.90~1.25)	age, race, education, insurance, region, DM, HTN, CVD, family history of kidney disease, HTN control
Vikse (2008) (Vikse et al., 2008)	Norway	retrospective cohort	1,120,789	<2,500 vs 2,501~4,499	1.50 (0.89~2.40)	sex, birth year, birth order, congenital malformation, multiple delivery, maternal factors (age, marital status, preeclampsia)
Ruggajo (2016) (Ruggajo et al., 2016)	Norway	retrospective cohort	322	<10th percentile vs >10th percentile	1.10 (0.52~2.40)	glomerular filtration
Eriksson (2018) (Eriksson et al., 2018)	Finland	cohort study	572	≤2,500 vs 3,000-3,499	1.00 (0.49~1.99)	unadjusted
Information for the relationship between low birth weight and CKD for female						
Lackland (2000) (Lackland et al., 2000)	USA	cross-control	1,014	<2,500 vs 3,000~3,499	1.90 (1.20~3.00)	unadjusted
Dyck (2003) (Dyck et al., 2003)	Canada	cross-control	130	<2,500 vs 2,501~3,999	2.70 (1.05~6.95)	unadjusted

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Salmi (2007) (Al Salmi et al., 2007)	Australia	cohort study	NA	<2,500 vs ≥2,500	2.04 (1.45~2.88)	unadjusted
Hallan (2008) (Hallan et al., 2008)	Norway	cohort study	3,923	<2,450 vs 2,870-4,190	1.01 (0.54~1.90)	age, smoking, education, maternal factors
Li (2008) (Li et al., 2008)	USA	retrospective cohort	9,444	<2,500 vs 3,000~3,999	1.07 (0.81~1.92)	age, race, education, insurance, region, DM, HTN, CVD, family history of kidney disease, HTN control
Vikse (2008) (Vikse et al., 2008)	Norway	retrospective cohort	1,061,909	<10th percentile vs 10 to 90th percentile	2.80 (1.80~4.40)	Sex, birth year, birth order, congenital malformation, multiple delivery, maternal factors (age, marital status, preeclampsia)
Ruggajo (2016) (Ruggajo et al., 2016)	Norway	retrospective cohort	139	<10th percentile vs >10th percentile	1.40 (0.32–6.40)	glomerular filtration
Eriksson (2018) (Eriksson et al., 2018)	Finland	cohort study	488	≤2,500 vs 3,000-3,499	1.99 (1.00~4.30)	unadjusted

690 Note: BMI: body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; HTN: hypertension; CVD: cerebrovascular disease; PSGN: post streptococcal glomerulonephritis.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

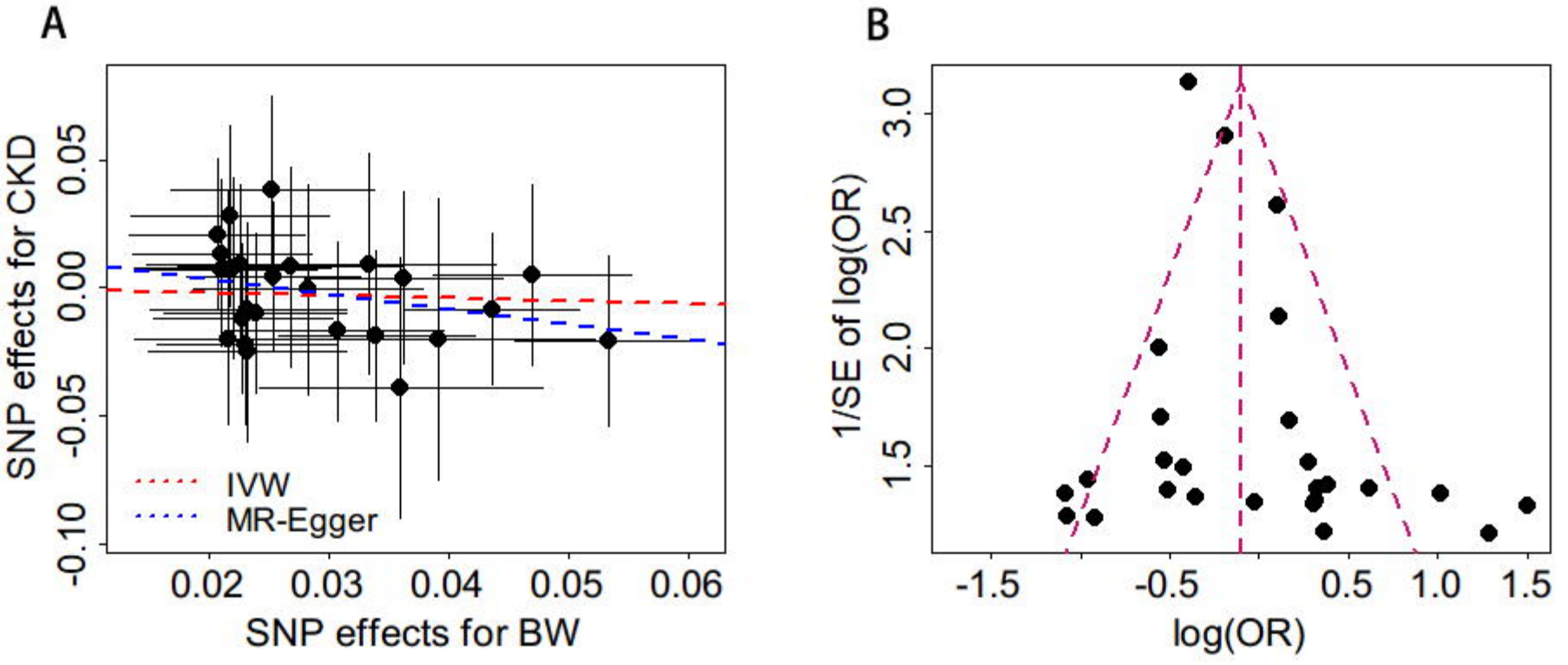
691 Fig. 1. Combined effect of birth weight on CKD in the meta-analysis based on
692 observational studies. (A) Combined effect for individuals with low birth weight
693 compared with those with normal birth weight based on twenty studies; (B) Combined
694 effect for individuals with high birth weight compared with those with normal birth
695 weight based on nine studies.

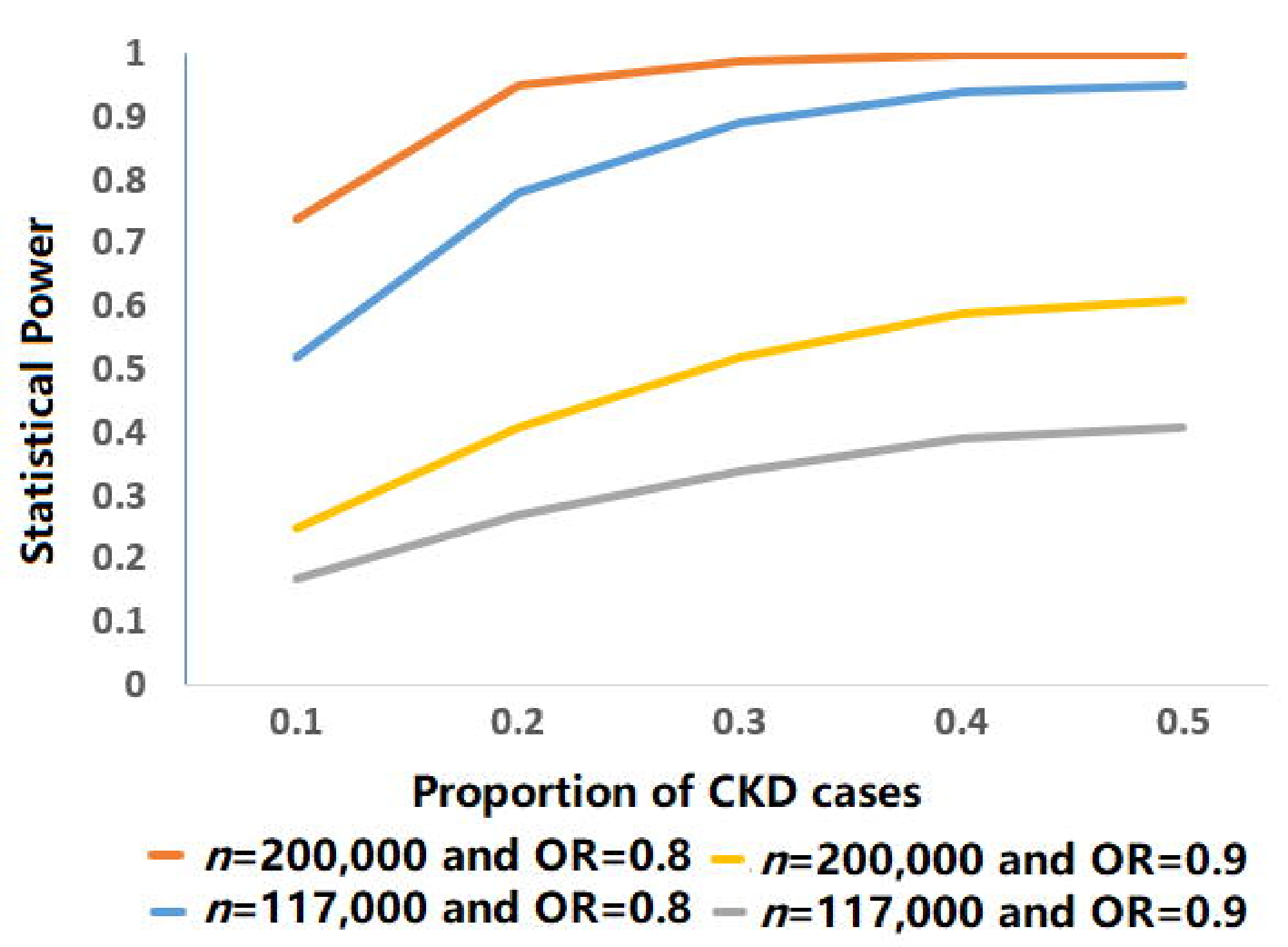
bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

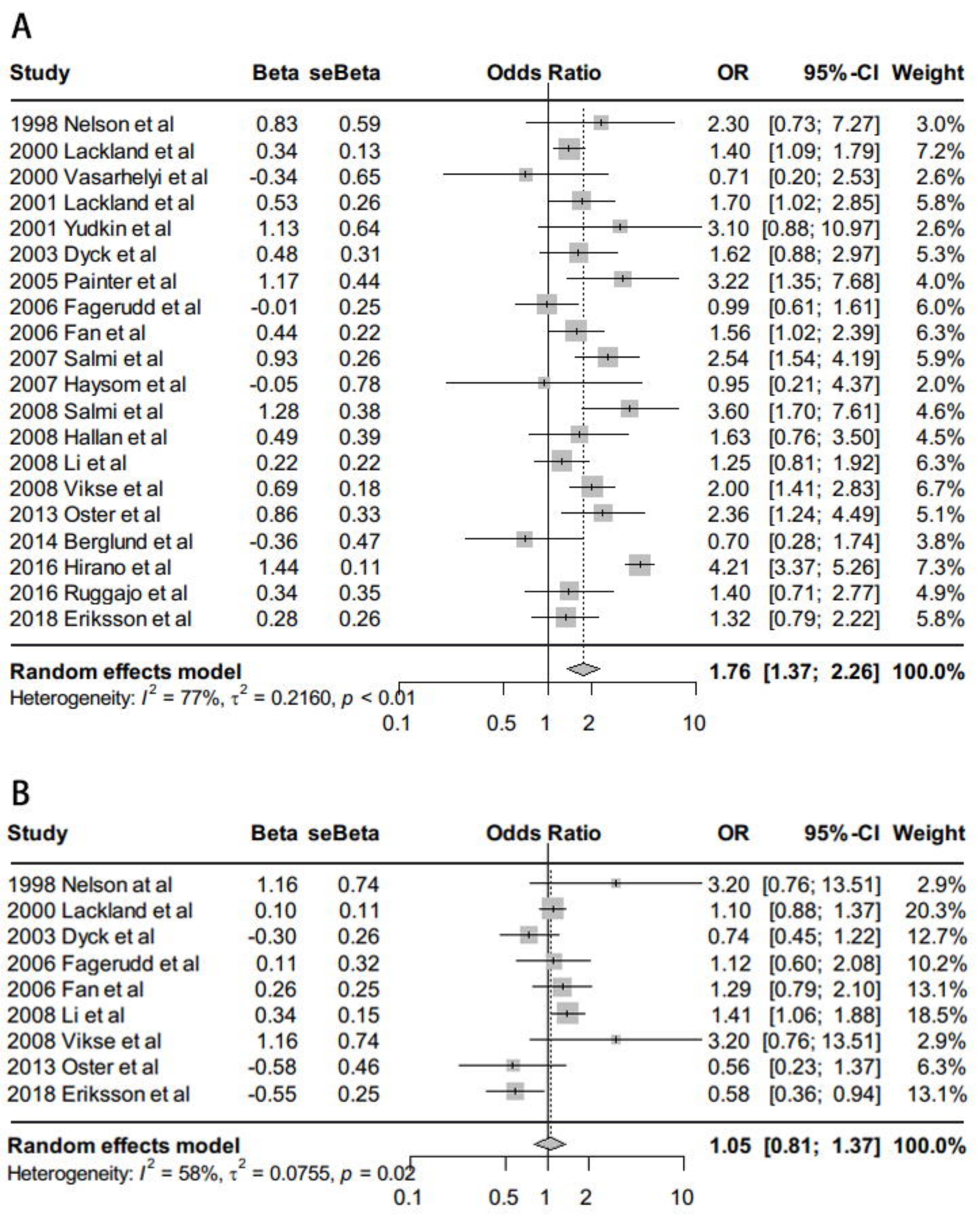
Fig. 2. (A) Relationship between the SNP effect size estimates of birth weight (x-axis) and the corresponding effect size estimates of CKD (y-axis). In the plot, the 95% CIs for the effect sizes of instruments on birth weight are shown as horizontal lines, while the 95% CIs for the effect sizes of instruments on CKD are shown as vertical lines. The line in red represents the estimated causal effect of birth weight on CKD obtained using the IVW method while the blue line represents the estimated causal effect produced by the MR-Egger regression. (B) Funnel plot for single causal effect estimate of birth weight on CKD; the horizontal dot line denotes the estimated causal effect with IVW.

bioRxiv preprint doi: https://doi.org/10.1101/729715; this version posted August 8, 2019. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

705 Fig. 3. Statistical power estimated with the analytic method shown in (Brion et al.,
706 2013). In the estimation, the total phenotypic variance explained by instrumental
707 variables was set to be 0.91%, the significance level α was set to be 0.05, the
708 proportion of CKD cases was set to be from 0.1 to 0.5. Two situations of sample size
709 (i.e. 117,000 and 200,000) were considered. For each situation, the OR was assumed
710 to be 0.80 or 0.90, respectively.


A
SNP effects for CKD
0.05
0.00
-0.05
-0.10
IVW
MR-Egger
0.02
0.03
0.04
0.05
0.06
SNP effects for BW
B
1/SE of log(OR)
3.0
2.5
2.0
1.5
-1.5
-0.5
0.5
1.0
1.5
log(OR)


Statistical Power
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.1
0.2
0.3
0.4
0.5
Proportion of CKD cases
n=200,000 and OR=0.8
n=200,000 and OR=0.9
n=117,000 and OR=0.8
n=117,000 and OR=0.9


A
Study
Beta
seBeta
Odds Ratio
OR
95%-CI
Weight
1998 Nelson et al 0.83 0.59 2.30 [0.73; 7.27] 3.0%
2000 Lackland et al 0.34 0.13 1.40 [1.09; 1.79] 7.2%
2000 Vasarhelyi et al -0.34 0.65 0.71 [0.20; 2.53] 2.6%
2001 Lackland et al 0.53 0.26 1.70 [1.02; 2.85] 5.8%
2001 Yudkin et al 1.13 0.64 3.10 [0.88; 10.97] 2.6%
2003 Dyck et al 0.48 0.31 1.62 [0.88; 2.97] 5.3%
2005 Painter et al 1.17 0.44 3.22 [1.35; 7.68] 4.0%
2006 Fagerudd et al -0.01 0.25 0.99 [0.61; 1.61] 6.0%
2006 Fan et al 0.44 0.22 1.56 [1.02; 2.39] 6.3%
2007 Salmi et al 0.93 0.26 2.54 [1.54; 4.19] 5.9%
2007 Haysom et al -0.05 0.78 0.95 [0.21; 4.37] 2.0%
2008 Salmi et al 1.28 0.38 3.60 [1.70; 7.61] 4.6%
2008 Hallan et al 0.49 0.39 1.63 [0.76; 3.50] 4.5%
2008 Li et al 0.22 0.22 1.25 [0.81; 1.92] 6.3%
2008 Vikse et al 0.69 0.18 2.00 [1.41; 2.83] 6.7%
2013 Oster et al 0.86 0.33 2.36 [1.24; 4.49] 5.1%
2014 Berglund et al -0.36 0.47 0.70 [0.28; 1.74] 3.8%
2016 Hirano et al 1.44 0.11 4.21 [3.37; 5.26] 7.3%
2016 Ruggajo et al 0.34 0.35 1.40 [0.71; 2.77] 4.9%
2018 Eriksson et al 0.28 0.26 1.32 [0.79; 2.22] 5.8%
Random effects model 1.76 [1.37; 2.26] 100.0%
Heterogeneity: I^2 = 77%, τ^2 = 0.2160, p < 0.01
0.1
0.5
1
2
10
B
Study
Beta
seBeta
Odds Ratio
OR
95%-CI
Weight
1998 Nelson at al 1.16 0.74 3.20 [0.76; 13.51] 2.9%
2000 Lackland et al 0.10 0.11 1.10 [0.88; 1.37] 20.3%
2003 Dyck et al -0.30 0.26 0.74 [0.45; 1.22] 12.7%
2006 Fagerudd et al 0.11 0.32 1.12 [0.60; 2.08] 10.2%
2006 Fan et al 0.26 0.25 1.29 [0.79; 2.10] 13.1%
2008 Li et al 0.34 0.15 1.41 [1.06; 1.88] 18.5%
2008 Vikse et al 1.16 0.74 3.20 [0.76; 13.51] 2.9%
2013 Oster et al -0.58 0.46 0.56 [0.23; 1.37] 6.3%
2018 Eriksson et al -0.55 0.25 0.58 [0.36; 0.94] 13.1%
Random effects model 1.05 [0.81; 1.37] 100.0%
Heterogeneity: I^2 = 58%, τ^2 = 0.0755, p = 0.02
0.1
0.5
1
2
10