Risk factors of chronic kidney disease progression: Dutch cohort studies

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Chapter 8 -

Low birth weight and kidney function in middle-aged men and women: The Netherlands Epidemiology of Obesity Study

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ABSTRACT

Rationale and objective: Chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, is a risk factor for cardiovascular morbidity and mortality. Little is known about low birth weight and the risk of CKD in middle-aged adults in the general population. Therefore, we investigated the association between birth weight and eGFR in a Dutch cohort of middle-aged men and women. We also studied the causal relation between birth weight and eGFR using genetic variants associated with birth weight as instrument.

Study design: observational study.

Setting and participants: 6,671 participants of the Netherlands Epidemiology of Obesity (NEO) study. Validation study with data on 133,814 participants of the CKDgen consortium.

Exposure: Birth weight was both self-reported, and based on an instrument, including 59 birth weight-associated genetic variants, derived from an independent data source.

Outcome: eGFR at the age of 45-65 years.

Analytical approach: We assessed the association between self-reported birth weight and eGFR in the NEO-study by multivariable linear regression, adjusted for age, sex, education, smoking, and alcohol use. The effect of the instrument for genetic low birth weight on eGFR was estimated by two separate two-sample Mendelian randomization analyses: with individual data from the NEO cohort and summary data from the CKDgen consortium.

Results: At baseline, mean (SD) eGFR was 86 (12.4) mL/min/1.73m^2. After multivariable adjustment, self-reported birth weight was not associated with kidney function at middle age. Two-sample Mendelian randomization analysis showed that in the NEO cohort each 500 gram genetically decreased birth weight was related to a 3.7 (95%-CI: 0.5; 6.9) mL/min/1.73m^2 lower kidney function at the age of 45-65 years. However, using CKDgen summary level data, showed no significant relation between birth weight and eGFR in middle-aged adults.

Limitations: Birth weight was self-reported.

Conclusion: Each 500 gram genetic lower birth weight was related with 3.7 ml/min/1.73m^2 lower kidney function at middle age. However, we could not validate this result in the CKDgen cohort.

INTRODUCTION

In Europeans ≥45 years, the prevalence of CKD, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, is high, at 11%.[1–3] CKD increases the risk of cardiovascular morbidity, mortality and end-stage renal disease (ESRD).[4] Classic cardiovascular risk factors, such as diabetes, smoking and hypertension can only explain part of the risk of CKD in adults. Therefore, identification of novel risk factors of CKD is important for targeted prevention of kidney function decline.

A low number of glomeruli at birth may predispose for CKD in adults. The number of glomeruli varies substantially across individuals, ranging from 300,000-2,000,000 per kidney.[5] Birth weight is a strong determinant for glomerular mass: each additional kg birth weight is associated with about 250,000 extra glomeruli per kidney.[5, 6] Human autopsy studies showed that a lower number of glomeruli was associated with a larger nephron volume, which suggests hyperfiltration.[6–8] Brenner hypothesized that adults with a congenital reduction in the number of glomeruli have a greater likelihood of developing hypertension and subsequent kidney failure.[9, 10] The mechanistic explanation for this phenomenon is that compensatory hyperfiltration by the remaining glomeruli results in accelerated kidney function decline. In addition, lower birth weight has been associated with increased insulin resistance, higher fasting insulin concentrations and increased incidence of type 2 diabetes mellitus.[11]

A recent meta-analysis, including almost 50,000 individuals from 31 studies, showed that low birth weight was associated with a 70% increased risk of CKD in adult life.[12] However, the majority of included studies consisted of highly selected samples of the population, consisting of subjects with diabetes, Pima Indians, or Aboriginals. It cannot be ruled out, that in the positive studies other factors caused both low birth weight and impaired kidney function later in life.

Since it is not known whether low birth weight causes lower kidney function in adults, we studied this relation from three perspectives. First, we examined the association between low birth weight and kidney function in a middle-aged cohort of the general Dutch population: the Netherlands Epidemiology of Obesity (NEO) study. Second, we performed a Mendelian randomization analysis in the NEO study, using a genetic risk score for low birth weight as an instrument in a causal analysis.[13] Finally, we validated the results from this Mendelian randomization analysis using summary level data of 133,814 individuals.[14, 15]

METHODS

Study design and participants

The Netherlands Epidemiology of Obesity (NEO) study is a population-based, prospective cohort study designed to investigate pathways that lead to common disorders. The NEO study included 6,671 individuals aged 45-65 years, with an oversampling of overweight or obese individuals. Men and women aged 45-65 years with a self-reported body mass index (BMI) ≥27 kg/m^2 living in the greater area of Leiden (in the West of the Netherlands) were eligible to participate. In addition, all inhabitants aged 45-65 years from one municipality (Leiderdorp) were invited to participate irrespective of their BMI, allowing a reference distribution of BMI. In total, 6,671 participants entered the study, of whom 5,000 with a BMI of 27 kg/m^2 or higher (Supplementary Figure S1). The study design and population are described in detail elsewhere.[16] The Medical Ethical Committee of the Leiden University Medical Center (LUMC) approved the design of the study (approval number P08.109). All participants gave written informed consent.

For the validation study we used data from 133,814 European participants of the CKDgen consortium. The CKDgen consortium includes data from 70 population-based studies, with a mean age between 50-60 years and a prevalence of CKD of 5-20%, defined as an eGFR <60 mL/min/1.73m^2.[14] This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[17]

Data collection

Participants were invited to a baseline visit at the NEO study centre of the LUMC after an overnight fast. At the baseline visit participants were physically examined, blood samples were drawn, medication was registered, and questionnaires regarding demographic, lifestyle, and clinical information, including birth weight, were obtained.[16] Patients were asked which of the following four broad categories of birth weight was applicable: <2.5, 2.5 to <3.0, 3.0 to <4.0, or ≥4.0 kg. We defined low birth weight as a birth weight <2.5 kg, according to the World Health Organization.[18]

Kidney function assessment

At baseline, serum creatinine was measured from fasting blood samples, by the Jaffé kinetic compensated method, or by the enzymatic method (isotope dilution mass spectrometry reference measurement procedure calibrated against standard reference material).[16] Serum Jaffé results were corrected with a fixed compensation factor of -26 µmol/L to compensate for assay non-specificity.

Creatinine-based glomerular filtration rate (eGFR) was estimated using the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, taking into account age, sex and race.[19] Urinary albumin was measured from spot morning urine samples. In men and women, moderately increased albuminuria was defined as 2.5-25 and 3.5-35 mg/mmol creatinine, and severely increased albuminuria as >25 and >35 mg/mmol creatinine, respectively.

Genetic instrument for birth weight

Genotyping was performed in participants of European ancestry only, using the Illumina HumanCoreExome-24 BeadChip (Illumina Inc., San Diego, California, USA). Genotypes were imputed to the 1000 Genome Project reference panel (v3 2011) using IMPUTE (v2.2) software.[20, 21] We excluded participants with poor genotype data (n=927): sample call rate <98%, sex mismatch, heterozygosity rate not within 3 SD of mean heterozygosity rate, duplicate samples, concordance between samples >0.25, or when participants differed based on the first two principal components (±3.5 SD).

In Mendelian randomization, genetic variants are proposed as instruments to estimate the causal effect of a risk factor (referred to here as an exposure) on an outcome, using observational data.[22] Genetic variants are assumed to be randomly distributed and become fixed at conception, mimicking the distribution of exposure in a randomized trial. Mendelian randomization thus bypasses the main limitation of observational studies: confounding and reverse causality. An instrument must meet the following assumptions: associated with the exposure of interest, only affect the outcome through the exposure (absence of horizontal pleiotropy), and not share any causes with the outcome and as such is independent of confounding factors (Figure 1A).[23] We additionally assume that the assumption of monotonicity holds, under which the causal estimate represents the average causal effect in the genetic "compliers".[24] In case of a continuous exposure, such as birth weight, compliers are those individuals in whom a higher value of the genetic instrument can only increase birth weight, or leave it constant.[24]

We used as instruments 59 autosomal genetic variants (single-nucleotide polymorphisms [SNPs]) reaching genome wide significance in European or trans-ancestry data in a recent genome-wide association study (GWAS) (Supplementary Table S1).[13] In total, these 59 SNPs explained approximately 2% of the birth weight variance. In the NEO-study, we calculated for each participant a weighted risk score by adding up for each individual SNP the number of coding alleles multiplied by their absolute effect on birth weight, based on European ancestry data reported by Horikoshi *et al.* (Figure 1B). As the weights were equal to the expected association of each variant with birth

weight in SDs, a 1-unit increase in genetic risk score corresponded to a 1-SD increase in genetically determined birth weight. which equals 500 gram of birth weight.[13, 25] For the CKDgen data, summary effects for each individual SNP were pooled into a causal estimate.

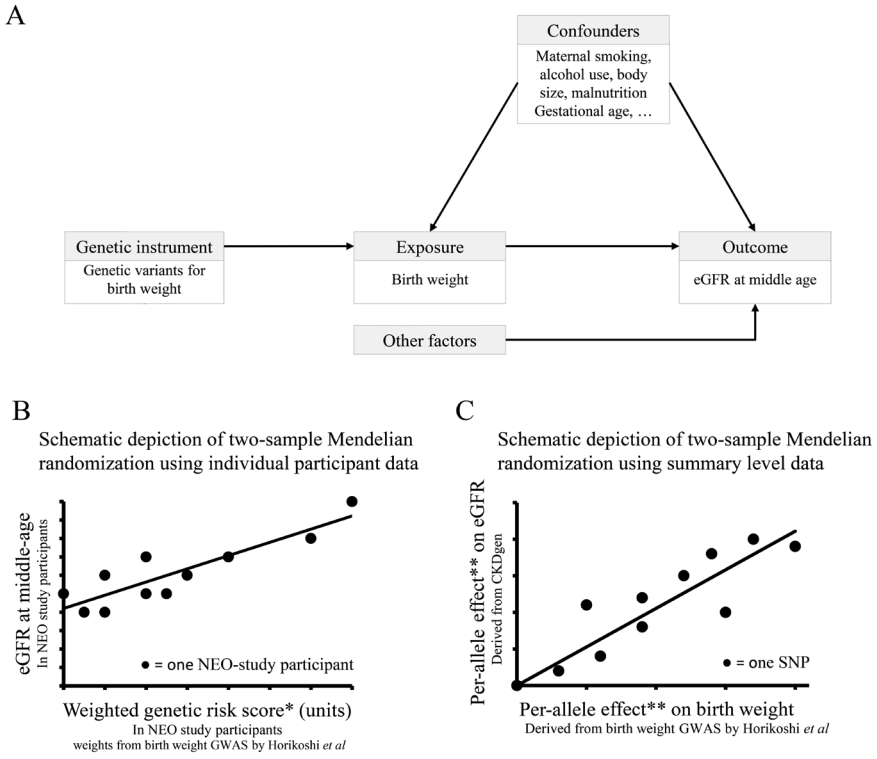

Figure 1: Graphical representation of Mendelian randomization assumptions (A), and schematic depiction of two-sample Mendelian randomization analyses using individual participant data (B) or summary level data (C). A) Basic scheme of the three assumptions of a genetic instrument: associated with the exposure of interest, associated with the outcome only through its association with the exposure and not via other factors, and independent of confounding factors. B) In the NEO cohort we calculated for each participant a weighted genetic risk score, with weights derived from the birth weight GWAS by Horikoshi *et al.*, and used linear regression to investigate the relation of the genetic risk score with eGFR at middle age. The relation is represented by the slope of the regression line. C) In case of two-sample Mendelian randomization using summary level data, for each SNP the per-allele effect on birth weight is contrasted to the per allele effect on eGFR. Both effects were derived from two different GWAS studies. The final causal estimate is represented by the slope of the regression line through all SNPs. *The weighted genetic risk score for every participated was calculated by summing up for each SNP the effect on birth weight multiplied by the number of risk alleles. ** Per-allele effects refer to the regression coefficients from univariable linear regression of the outcome of interest (eGFR) or birth weight, for each SNP.

Statistical analyses

All analyses involving NEO study participants were weighted towards the BMI distribution of the general population, to adjust for the oversampling of individuals with a BMI ≥27 kg/m^2.[26] The weighing procedure is described in detail in Supplementary Figure S2. Baseline characteristics were presented as mean (SD), median (25th - 75th percentile) or percentage, for all participants and across birth weight strata. Assuming missingness was at random, we used multiple imputation for the main analyses. Multiple imputation generally results in less bias than analyzing complete cases only.[27] Missing values were imputed for birth weight (36%), education (1.0%), eGFR (0.7%), urinary albumin (0.4%), ethnicity (0.2%), smoking (0.1%), and alcohol use (<0.1%). We used 10 imputations, including all relevant variables and the outcome into the model. Standard errors of pooled estimates were derived using Rubin's rules.[28] As sensitivity analysis we performed a complete case analysis.

We performed linear regression to examine the relation between self-reported birth weight and eGFR or urinary albumin-to-creatinine ratio (UACR). Logistic regression was used to examine the relation between birth weight and risk of CKD stage 3 (eGFR <60 mL/min/1.73m^2) or albuminuria. Analyses were adjusted for age and sex (model 1). In model 2, we adjusted in addition to model 1, for ethnicity and level of education (high *vs* low). In model 3, we adjusted in addition to model 2, for smoking (current, former, or never) and alcohol consumption (g/day). Finally, we repeated all analyses restricted to Caucasian individuals.

In addition, we conducted two separate two-sample Mendelian randomization analyses, using individual participant data and summary level data. In two-sample Mendelian randomization, the associations between instrument-exposure and instrument-outcome are derived from two different populations or data sources.[15] First, we performed a two-sample Mendelian randomization analysis using individual participant data from the NEO-study (Figure 1B). In this analysis the instrument data were derived from Horikoshi *et al.* and the outcome data from the NEO-study. We used ordinal logistic regression taking birth weight as outcome, to verify the validity of the genetic risk score as instrument for birth weight. We compared age, sex, educational level, diabetes, and obesity across quartiles of the genetic risk score. Subsequently, linear regression was used to quantify the effect of the genetic risk score for birth weight on eGFR at middle age, adjusted for age, sex, and the four most prominent principal components of ancestry.

Second, we performed a two-sample Mendelian randomization analysis using summary level data from the CKDgen consortium. In this analysis instrument-exposure data were derived from Horikoshi *et al.* and the

instrument-outcome data were derived from the CKDgen consortium (Figure 1C).[13, 14] A major advantage of two-sample Mendelian randomization using summary statistics is the increased power. In case of missing SNPs, LD proxies were used ($R^2 > 0.8$) when available, using the 1000 Genomes European sample data in SNAP Proxy Search (Supplementary Table S1 and S2).[29] The presence of LD between SNPs was excluded (n=3) using a threshold of $R^2 > 0.001$). Ultimately, 45 SNPs, including proxies, were available in the CKDgen data. The median (25th – 75th percentile) F-statistic for all 59 SNPs was 35.5 (30.9 – 44.4) and for the 45 SNPs in CKDgen was 33.2 (30.8 – 43.6). Instruments with an F-statistic >10 are generally assumed sufficiently strong to avoid weak instrument bias.[30] The pooled causal estimate in summary level analyses was calculated by regressing the SNP-eGFR effect derived from the CKDgen data on the SNP-birth weight effect derived from Horikoshi *et al.*, weighted by the precision of the SNP-eGFR effect, and with the intercept constrained to zero (Figure 1C).[13, 14] The pooled causal estimate represents the effect of a 1-SD (about 500 gram) increment of genetically increased birth weight on log-transformed eGFR. The IVW method assumes zero horizontal pleiotropy and uses weights that assume no measurement error for the association between SNPs and birth weight.[31, 32]

In addition, we performed several sensitivity analyses. First, we visually examined directional horizontal pleiotropy by leave-one-out and funnel plot analyses. Second, we performed MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analyses, which tests for directional horizontal pleiotropy (MR-PRESSO global test) and detects and corrects for outliers.[33] Third, MR-Egger intercept test was performed, which allows the intercept to deviate from zero to indicate pleiotropy.[32] The intercept from the MR-Egger test can be interpreted as the average pleiotropic effect of all SNPs.[34] The slope of the MR-Egger regression analysis represents the pleiotropy-corrected causal effect. Fourth, we used the weighted median and weighted mode methods. Both methods are less sensitive to outliers, compared to mean-based approaches such as the IVW and MR-Egger method. The weighted median method provides consistent estimates, regardless of horizontal pleiotropy, if at least 50% of the information comes from valid instruments.[35] The weighted mode estimator requires that the most common causal effect estimate comes from valid instruments, even if the majority of instruments is invalid.[36] Finally, a GWAS may not only tag fetal genes associated with birth weight, but also maternal genes, which may influence birth weight through effects on the intrauterine environment. To reduce potential maternal effects of birth weight SNPs, we repeated the analyses excluding SNPs where the maternal effects were strongly associated with birth weight, as reported by Horikoshi *et al.* As threshold we used a Bonferroni corrected p-value of 0.0011 for the maternal association between

each SNP and birth weight, based on 45 SNPs. Analyses in the NEO-study were performed using STATA Statistical Software version 14 (Statacorp, Texas, USA). Two-sample Mendelian randomization analyses using summary level data were performed in R version 3.4.3 (R Foundation for Statistical Computation, Vienna, Austria) using the *TwoSampleMR* and *MR-PRESSO* packages.[33, 37]

RESULTS

Baseline characteristics

Baseline data of all participants and according to four categories of birth weight are presented in Table 1. Mean (SD) eGFR of all participants was 86.2 (12.4) mL/min/1.73m^2. The prevalence of moderately and severely increased albuminuria, and CKD was 2.2%, 0.8%, and 2.2%, respectively. Participants with lower birth weight were more often female, had a lower level of education, had more comorbid conditions, and used more medication. Participants with low birth weight were less likely Caucasian. About 3.2% of all participants with birth weight <2.5 kg were from East-Asian origin. Other ethnic backgrounds were equally distributed across categories of birth weight.

Table 1: Baseline characteristics of 6,671 middle-aged participants of the Netherlands Epidemiology of Obesity study.

		Birth weight (kg)			
	Total population n=6,671	<2.5 (11%)	2.5 to <3.0 (25%)	3.0 to <4.0 (49%)	≥4.0 (15%)
Demographic/anthropometric					
Age (y)	55.7 (6.0)	55.8 (6.1)	55.9 (5.5)	54.9 (6.1)	55.0 (6.4)
Sex (% men)	43.6	29.2	35.2	40.9	52.3
Ethnicity (% Caucasian)	94.9	92.6	96.5	97.7	97.5
Education level (% high)	45.9	38.2	40.5	50.5	51.1
Body-mass index (kg/m^2)	26.3 (4.5)	26.0 (4.4)	25.7 (4.3)	26.1 (4.3)	26.8 (5.4)
Waist circumference (cm)					
Men	98.4 (11.4)	97.1 (9.7)	96.2 (11.4)	97.3 (10.9)	99.9 (13.3)
Women	87.4 (12.6)	87.1 (12.7)	85.6 (12.5)	86.8 (12.3)	86.9 (12.9)
Total body fat (%)					
Men	25.0 (6.1)	24.9 (5.1	24.2 (6.2)	24.5 (5.8)	25.3 (6.8)
Women	36.9 (6.4)	36.3 (6.7)	35.7 (6.9)	36.8 (6.3)	37.0 (7.0)
Current smoking (%)	16.0	15.2	15.6	15.0	16.3
Alcohol intake (g/d)	14.7 (16.3)	11.5 (12.4)	14.4 (16.1)	15.0 (15.6)	14.2 (17.1)
Comorbidity (%)					
Diabetes[a]	5.7	6.5	4.2	4.8	4.2
Heart failure	0.5	1.3	0.4	0.4	0.2
Hypertension	34.0	39.1	36.8	29.6	33.0
Hypercholesterolemia	13.2	16.2	13.9	11.5	9.8
Chronic kidney disease[b]	2.2	2.0	2.3	1.8	1.4
Medication use (%)					
BP-lowering drugs	23.5	28.0	23.1	21.2	19.3
RAS-blockers	13.9	17.8	12.3	12.3	10.9

Table 1: Continued

	Total population n=6,671	Birth weight (kg)			
		<2.5 (11%)	2.5 to <3.0 (25%)	3.0 to <4.0 (49%)	≥4.0 (15%)
Glucose-lowering drugs	2.8	3.3	2.2	2.1	1.7
Statins	10.5	13.5	9.8	8.5	7.0
Laboratory measurements					
Fasting glucose[c] (mg/dL)	99 (18)	99 (16)	97 (14)	97 (18)	97 (16)
Total cholesterol[d] (mg/dL)	220 (43)	220 (39)	224 (39)	220 (39)	217 (43)
HDL cholesterol[d] (mg/dL)	62 (19)	62 (15)	62 (15)	62 (15)	62 (23)
LDL cholesterol[d] (mg/dL)	135 (39)	139 (39)	139 (35)	135 (35)	135 (43)
Serum creatinine[e] (mg/dL)	0.87 (0.16)	0.84 (0.15)	0.85 (0.15)	0.86 (0.16)	0.88 (0.17)
eGFR[f] (mL/min/1.73m^2)	86.2 (12.4)	85.9 (12.2)	85.7 (11.8)	86.6 (12.3)	87.0 (13.2)
Urinary albumine (mg/L)	3.6 (3.0–4.8)	3.6 (3.0–5.0)	3.6 (3.0–4.9)	3.6 (3.0–4.8)	3.6 (3.0–4.9)
UACR (mg/mmol)	0.4 (0.3–0.7)	0.5 (0.3–0.8)	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.4 (0.3–0.7)
Albuminuria (%)					
Moderately increased	2.2	3.5	2.2	2.0	1.3
Severely increased	0.8	0.0	0.9	0.9	0.7

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin-angiotensin system; UACR, urinary albumin to creatinine ratio.
Results were based on analyses weighted towards the BMI distribution of the general population. The number of participants with available birth weight data was 4,250.
Results are shown as mean (SD), median (IQR), or percentage in the total study population as well as stratified per birth weight category.
[a] Defined as self-reported diagnosis, or serum fasting glucose levels ≥126 mg/dL.
[b] Defined as eGFR <60.0 mL/min/1.73m^2.
[c] To convert the values for glucose to mmol/L, multiply by 0.05551.
[d] Estimated using the Friedewald formula. To convert the values for LDL-cholesterol to mmol/L, multiply by 0.02586.
[e] To convert the values for serum creatinine to µmol/L, multiply by 88.40.
[f] eGFR was estimated using the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

Birth weight and kidney function

We found no differences in eGFR across the four birth weight categories (Table 2). After multivariable adjustment, we observed no association between birth weight and risk of CKD stage 3 or albuminuria. Restricting analyses to cases with complete data (Supplementary Table S3), or Caucasian individuals (Supplementary Table S4), did not essentially change the results.

Table 2: Difference in kidney function, urinary albumin-to-creatinine ratio, risk of CKD, and albuminuria, according to birth weight categories at age 45-65 years in 6,671 participants of the Netherlands Epidemiology of Obesity study.

Birth weight (kg)	Crude	Model 1	Model 2	Model 3
		Difference in eGFR		
<2.5	-0.91 (-2.62; 0.80)	0.21 (-1.78; 1.36)	-0.45 (-2.02; 1.12)	-0.41 (-1.98; 1.16)
2.5 to <3.0	-0.84 (-2.19; 0.52)	-0.25 (-1.50; 1.00)	-0.36 (-1.61; 0.89)	-0.37 (-1.60; 0.86)
3.0 to <4.0 (ref)	0	0	0	0
≥4.0	0.51 (-1.07; 2.10)	0.42 (-1.10; 1.93)	0.44 (-1.07; 1.95)	0.45 (-1.05; 1.95)
		Difference in UACR		
<2.5	-0.03 (-0.51; 0.46)	-0.04 (-0.53; 0.45)	-0.10 (-0.61; 0.40)	-0.10 (-0.60; 0.40)
2.5 to <3.0	0.11 (-0.28; 0.51)	0.10 (-0.30; 0.50)	0.07 (-0.32; 0.45)	0.07 (-0.31; 0.45)
3.0 to <4.0 (ref)	0	0	0	0
≥4.0	0.27 (-0.34; 0.88)	0.26 (-0.36; 0.89)	0.27 (-0.36; 0.90)	0.25 (-0.37; 0.88)
		Odds ratio for CKD [a]		
<2.5	1.18 (0.46; 3.00)	0.99 (0.39; 2.52)	0.99 (0.38; 2.54)	0.98 (0.39; 2.51)
2.5 to <3.0	1.37 (0.75; 2.50)	1.24 (0.69; 2.26)	1.24 (0.68; 2.25)	1.23 (0.69; 2.22)
3.0 to <4.0 (ref)	1	1	1	1
≥4.0	0.77 (0.36; 1.65)	0.80 (0.37; 1.74)	0.80 (0.37; 1.75)	0.78 (0.36; 1.68)
		Odds ratio for moderately or severely increased albuminuria [b]		
<2.5	1.16 (0.59; 2.30)	1.30 (0.65; 2.60)	1.21 (0.60; 2.47)	1.25 (0.61; 2.55)
2.5 to <3.0	1.14 (0.68; 1.91)	1.20 (0.72; 2.01)	1.14 (0.68; 1.91)	1.14 (0.69; 1.89)
3.0 to <4.0 (ref)	1	1	1	1
≥4.0	0.85 (0.46; 1.56)	0.77 (0.42; 1.42)	0.78 (0.41; 1.47)	0.78 (0.42; 1.46)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio. * p<0.05.
Results were based on analyses weighted towards the BMI distribution of the general population.
Mean (SD) baseline eGFR in the reference group is 86.6 (12.3) mL/min/1.73m^2. Median (IQR) baseline UACR in the reference group is 0.45 (0.30; 0.71) mg/g.
[a] Analyses were weighted towards the BMI distribution of the general population, therefore no absolute numbers were presented. The prevalence of CKD was 2.2%.
[b] Analyses were weighted towards the BMI distribution of the general population, therefore no absolute numbers were presented. The prevalence of albuminuria was 3%.
Model 1: adjusted for age and sex.
Model 2: Model 1, additionally adjusted for race and level of education.
Model 3: Model 2, additionally adjusted for cigarette smoking and alcohol consumption.

Two-sample Mendelian randomization using individual participant data

The proportion of participants with a high birth weight (≥4000 gram) increased for each incremental quartile of the genetic risk score (Table 3). Ordinal logistic regression analyses showed that each 1-SD increase in genetic risk score was associated with a 2.9 (95% CI 1.5; 5.5, p=0.001) fold increased risk of being in a higher birth weight category. After multivariable adjustment, each 500 gram decrease in genetically determined birth weight was related to a 3.7 (95% CI: 0.5; 6.9, p=0.025) mL/min/1.73m^2 lower eGFR at middle age. The genetic risk score was not associated with age, sex, educational level, or obesity (Supplementary Table S5). Overall, the proportion of participants with diabetes was low (6%), and slightly decreased in higher quartiles of the genetic risk score. We found no relation between the genetic risk score and proteinuria: per 500 gram decrease in genetically determined birth weight the UACR decreased by 0.08 mg/mmol (p=0.8).

Table 3: According to quartiles of the genetic risk score, the proportion of participants within incremental categories of birth weight in participants of the Netherlands Epidemiology of Obesity study.

	Genetic risk score	
Birth weight (kg)	Quartile 1 (<2.17)	Quartile 4 (≥2.36)
<2.5	11.9	9.1
2.5 to <3.0	25.9	22.1
3.0 to <4.0	50.0	49.1
≥4.0	12.3	19.8

Results were based on analyses weighted towards the BMI distribution of the general Dutch population.

Two-sample Mendelian randomization using summary level data

We found no significant relation between genetically determined birth weight and creatinine based eGFR using summary level data from the CKDgen consortium (Figure 2, Table 4). The pooled effect per 1-SD genetically increased birth weight (about 500g) on log-transformed eGFR was 0.009 (-0.002; 0.019, p=0.11), which equals a 1.01% higher eGFR. Thus at middle age, each 500 gram genetically decreased birth weight was related to a 1% lower eGFR. After excluding 20 SNPs (Supplementary Table S1) with strong maternal effects, we found slightly weaker results: IVW estimator 0.004 (-0.009; 0.018, p=0.5). Leave-one-out analysis and funnel plot analysis were not suggestive for directional horizontal pleiotropy (Supplementary Figure S3 and S4). The MR-Egger intercept test indicated no directional horizontal pleiotropy (p=0.37). MR-PRESSO indicated no directional horizontal pleiotropy (p=0.20) and detected no outliers. Results of the weighted median and mode method were comparable to the IVW method (Table 4).

Table 4: Causal effect per 500 gram genetically increased birth weight on log-transformed eGFR at middle age, by different instrumental variable estimators.

Estimator	Beta	Standard error	p-value
Inverse variance weighted	0.0088	0.0055	0.11
Weighted median	0.0133	0.0072	0.06
Weighted mode	0.0157	0.0107	0.15
MR-Egger (intercept)	-0.0005	0.0006	0.37
MR-Egger (slope)	0.0253	0.0191	0.19

The Beta coefficient is the pooled causal estimate from the two-sample summary data Mendelian randomization analyses, and should be interpreted as the effect per 500 gram genetically increased birth weight on log-transformed eGFR.
MR-PRESSO analysis did not show evidence for directional horizontal pleiotropy (p=0.20), and did not detect any statistically significant (threshold p<0.05) outliers.

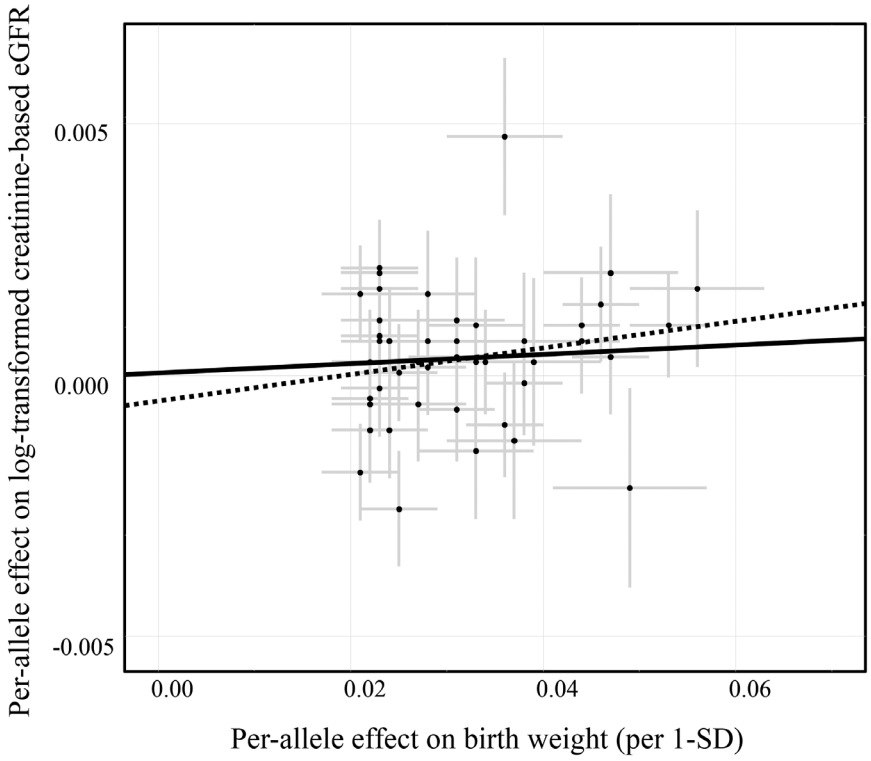

Figure 2: Per-allele effects (95%-CI) on the outcome plotted against per-allele effects (95%-CI) on the exposure. The slope of the line represents the causal association. The slope of the inverse-variance weighted line (solid line) was 0.009 (SE 0.0055, p=0.11), and for the MR-Egger (dotted line) was 0.025 (SE 0.019, p=0.19). The intercepts and slopes of the inverse-variance weighted method and MR-Egger method differ only slightly, which is confirmed by a non-significant p-value for horizontal pleiotropy (p=0.37).
MR, Mendelian randomization; SNP, single nucleotide polymorphism

DISCUSSION

In a Dutch population-based cohort of middle-aged mainly Caucasian adults, self-reported birth weight was not associated with kidney function. In contrast, two-sample Mendelian randomization analysis, showed that each 500 gram of genetically decreased birth weight was related with a 3.7 mL/min/1.73m^2 lower kidney function at middle-age in a Dutch cohort. However, we could not validate this finding in the CKDgen consortium data including 133,814 individuals, showing a small but not significant effect of genetically lower birth weight on kidney function: 1% lower eGFR per 500 gram lower birth weight.

Our results are not in line with a large meta-analysis (including 31 studies), stating that low birth weight increases the risk of CKD and ESRD.[12] However, this meta-analysis included only 2 studies representative for the general adult population. Due to high heterogeneity of included studies, suboptimal and incomplete birth weight data collection, and difficulties pooling all included studies, estimates may have been inflated.

The Nord Trøndelag Health (HUNT 2) study explored the association of birth weight with kidney function at age 20-30 years among 7,457 individuals from the general population. Its main strength was the accurate measurement of birth weight.[38] The authors of the HUNT 2 study showed that in men each additional kg of birth weight was associated with an additional eGFR increase of 1.0 (-0.1; 2.1) mL/min/1.73m^2, after adjusting for maternal factors. In women there was no association between birth weight and kidney function. The discrepancy between our results and those of the HUNT-2 study may be related to the different ages of the cohorts (20-30y *vs* 45-65y). In general, after age 40y there is an age-related annual kidney function decline of 1.0 mL/min/1.73m^2.[39, 40] In addition, risk factors such as diabetes, hypertension and smoking may accelerate kidney function decline. Taken together, the age-related kidney function decline and known risk factors of accelerated kidney function decline, may have diluted any effect of low birth weight in our older cohort of the NEO study.

Our observational cohort study has several limitations. First, birth weight of NEO-study participants was collected by means of questionnaires at the age of 45-65. Most likely, this may have led to measurement error of birth weight resulting in non-differential misclassification. In general, non-differential misclassification results in underestimation of the association between birth weight and eGFR.[41] Therefore, we performed Mendelian randomization analyses to avoid measurement error of birth weight in the NEO-study. Second, eGFR was not measured directly, but was estimated by the CKD-EPI equation, which may underestimate kidney function in participants with an eGFR higher than 90 mL/min/1.73m^2.[42] However, measured GFR is rarely available in large epidemiological studies, and even daily iothalamate measurements can vary up to 8%.[43] Third, we assessed middle-aged individuals, in whom age-related kidney function decline together with other risk factors of accelerated kidney function decline may have diluted any effect of low birth weight. Fourth, for smaller individuals, a "low" birth weight may be regarded as normal in relation to an individual's body mass and circulating volume. This is not taken into account by currently used absolute cut-offs for low birth weight. Finally, we had no information about confounding factors such as gestational age, and lifestyle during pregnancy such as cigarette smoking, alcohol use, and malnutrition.

These factors are important causes of low birth weight, and not taking them into account could lead to overestimation of a potential negative effect of low birth weight. However, in our study we found no relevant association between low birth weight and kidney function.

Limitations of our Mendelian randomization analyses are mainly related to the used instrument. First, the GWAS investigating SNPs associated with birth weight excluded individuals with a birth weight <2.5 kg and >4.5 kg from part of the used data sources. This may have resulted in exclusion of SNPs associated with low or high birth weight. Second, some of the SNPs could have an effect via a maternal pathway, rather than direct fetal effects on birth weight. However, Horikoshi *et al.* showed that the fetal genetic variation had a greater impact on birth weight than maternal variation at 55/59 genetic loci.[13] Excluding SNPs with strong maternal effects did not change our results. Third, the Mendelian randomization assumption of no directional horizontal pleiotropy requires that an instrument affects the outcome only via the exposure of interest (birth weight), and not via other mechanisms. An instrument consisting of 59 different SNPs may therefore be particularly prone to directional horizontal pleiotropy. However, MR-Egger and MR-PRESSO analyses showed no evidence for directional horizontal pleiotropy. Fourth, our genetic instrument explained only 2% of the birth weight variance, which may result in limited power. Importantly, confidence intervals were informative both in the NEO-study and in the CKDgen data, which implies sufficient power in both cases. Fifth, using many genetic instruments increases the risk of weak instrument bias. If an instrument is weak, any association between the instrument and the outcome may be explained by unbalanced confounders, rather than by the instrument itself.[30] In the present study, the instruments were chosen based on a large-scale independent genome-wide association study on birth weight, which is reflected by the high F-statistics (F >10). Of note, patient overlap between populations may hamper the interpretation of bias in case of weak instruments. In the present study, there was 2.8% overlap of participants between Horikoshi *et al.* and the NEO study, and 4.6% between Horikoshi *et al.* and the CKDgen consortium. Given the relatively small proportion of overlap, and the sufficiently strong instruments that we used, any influence of weak instrument bias is most likely negligible.

The most important strength of our study is that we used three complementary approaches.- We performed an observational study with a large sample, representative for the general population. For the two-sample Mendelian randomization analyses we used an instrument based on a previously validated genetic score for birth weight, and we validated our findings in the NEO-study using summary level data of the CKDgen consortium.

Self-reported birth weight was not associated with kidney function. In contrast, each 500 gram of genetically decreased birth weight was related with a 3.7 mL/min/1.73m^2 lower kidney function at middle-age in a Dutch cohort. However, we could not validate this finding in another cohort of the CKDgen consortium.

ARTICLE INFORMATION

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AUTHORS' CONTRIBUTIONS

Research idea and study design: EH, KE, AV, RM, FR, DM; data acquisition: KE, RM, FR, DM, TR; data analysis/interpretation: KE, EH, DM, RM, FR, RS, JF; statistical analyses: KE, EH, DM; RS supervision or mentorship: EH, DM, JF. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

REFERENCES

1. Wetmore JB, Collins AJ. Global challenges posed by the growth of end-stage renal disease. *Renal Replacement Therapy.* 2016; 2: 15.
2. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. *World Health Organ Tech Rep Ser.* 2000: 894: 839-868.
3. Bruck K, Stel VS, Gambaro G, et al. CKD Prevalence Varies across the European General Population. *J Am Soc Nephrol.* 2016; 27: 2135-2147.
4. Vanholder R, Massy Z, Argiles A, et al. Chronic kidney disease as cause of cardiovascular morbidity and mortality. Nephrol Dial Tran*splant.* 2005; 20: 1048-1056.
5. Puelles VG, Hoy WE, Hughson MD, et al. Glomerular number and size variability and risk for kidney disease. *Curr Opin Nephrol Hypertens.* 2011; 20: 7-15.
6. Hughson M, Farris AB, 3rd, Douglas-Denton R, Hoy WE, Bertram JF. Glomerular number and size in autopsy kidneys: the relationship to birth weight. *Kidney Int.* 2003; 63: 2113-2122.
7. Hoy WE, Hughson MD, Zimanyi M, et al. Distribution of volumes of individual glomeruli in kidneys at autopsy: association with age, nephron number, birth weight and body mass index. *Clin Nephrol.* 2010; 74 Suppl 1: S105-112.
8. Manalich R, Reyes L, Herrera M, Melendi C, Fundora I. Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney Int.* 2000; 58: 770-773.
9. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int.* 1996; 49: 1774-1777.
10. Silverwood RJ, Pierce M, Hardy R, et al. Low birth weight, later renal function, and the roles of adulthood blood pressure, diabetes, and obesity in a British birth cohort. *Kidney Int.* 2013; 84: 1262-1270.
11. Newsome CA, Shiell AW, Fall CH, et al. Is birth weight related to later glucose and insulin metabolism?--A systematic review. *Diabet Med.* 2003; 20: 339-348.
12. White SL, Perkovic V, Cass A, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am J Kidney Dis.* 2009; 54: 248-261.
13. Horikoshi M, Beaumont RN, Day FR, et al. Genome-wide associations for birth weight and correlations with adult disease. *Nature.* 2016; 538: 248-252.
14. Pattaro C, Teumer A, Gorski M, et al. Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. *Nat Commun.* 2016; 7: 10023.
15. Lawlor DA. Commentary: Two-sample Mendelian randomization: opportunities and challenges. *Int J Epidemiol.* 2016; 45: 908-915.

16. de Mutsert R, den Heijer M, Rabelink TJ, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. *Eur J Epidemiol.* 2013; 28: 513-523.
17. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. *PLoS Med.* 2007; 4: e297.
18. World Health Organization. International statistical classification of diseases and related health problems, 10th revision. Geneva, Switzerland: World Health Organization; 2016.
19. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012; 367: 20-29.
20. Abecasis GR, Auton A, Brooks LD, et al. An integrated map of genetic variation from 1,092 human genomes. *Nature.* 2012; 491: 56-65.
21. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet.* 2007; 39: 906-913.
22. Smit RA, Trompet S, de Craen AJ, Jukema JW. Using genetic variation for establishing causality of cardiovascular risk factors: overcoming confounding and reverse causality. *Neth Heart J.* 2014; 22: 186-189.
23. Boef AG, Dekkers OM, le Cessie S. Mendelian randomization studies: a review of the approaches used and the quality of reporting. *Int J Epidemiol.* 2015; 44: 496-511.
24. Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. *Eur J Epidemiol.* 2018; 33: 947-952.
25. Walter S, Mejía-Guevara I, Estrada K, Liu SY, Glymour MM. Association of a Genetic Risk Score With Body Mass Index Across Different Birth Cohorts *JAMA.* 2016; 316: 63-69.
26. Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. *Am J Public Health.* 1991; 81: 1166-1173.
27. Janssen KJ, Donders AR, Harrell FE, Jr., et al. Missing covariate data in medical research: to impute is better than to ignore. *J Clin Epidemiol.* 2010; 63: 721-727.
28. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2010; 30: 377-399.
29. Johnson AD, Handsaker RE, Pulit SL, et al. SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap. *Bioinformatics.* 2008; 24: 2938-2939.
30. Burgess S, Thompson SG, Collaboration CCG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol.* 2011; 40: 755-764.
31. Bowden J, Del Greco M F, Minelli C, et al. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med.* 2017; 36: 1783-1802.
32. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol.* 2017; 32: 377-389.

33. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet.* 2018; 50: 693-698.
34. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol.* 2015; 44: 512-525.
35. Bowden J, Davey Smith G, Haycock Philip C, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet Epidemiol.* 2016; 40: 304-314.
36. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol.* 2017; 46: 1985-1998.
37. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *eLife.* 2018; 7: e34408.
38. Hallan S, Euser AM, Irgens LM, et al. Effect of intrauterine growth restriction on kidney function at young adult age: the Nord Trondelag Health (HUNT 2) Study. *Am J Kidney Dis.* 2008; 51: 10-20.
39. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc.* 1985; 33: 278-285.
40. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *J Gerontol.* 1976; 31: 155-163.
41. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. *Br med J.* 2010 ;340: c2289.
42. MacIsaac RJ, Ekinci EI, Premaratne E, et al. The Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation does not improve the underestimation of Glomerular Filtration Rate (GFR) in people with diabetes and preserved renal function. *BMC Nephrol.* 2015; 16: 198-210.
43. Kwong YT, Stevens LA, Selvin E, et al. Imprecision of urinary iothalamate clearance as a gold-standard measure of GFR decreases the diagnostic accuracy of kidney function estimating equations. *Am J Kidney Dis.* 2010; 56: 39-49.

SUPPLEMENTARY DATA

Table S1: Genetic variants (n=59) associated with birth weight adapted from the genome-wide association study by Horikoshi *et al.*[1] We included these variants in a genetic risk score that we used as instrument for birth weight.

SNP		Gene	Chr	ffect/other allele	Beta*	SE	EAF	R^2 (%) **	F-stat ***
rs2473248		WNT4-ZBTB40	1	C/T	0.033	0.006	0.87	0.024	33.3
rs3753639	b	ZBTB7B	1	C/T	0.031	0.004	0.23	0.034	47.2
rs72480273		FCGR2B	1	C/A	0.031	0.005	0.36	0.028	38.3
rs61830764	c	DTL	1	A/G	0.022	0.004	0.17	0.023	31.5
rs7575873		ATAD2B	2	A/G	0.038	0.006	0.88	0.031	43.4
rs1374204	d	EPAS1	2	T/C	0.047	0.004	0.70	0.093	124.9
rs2242116	d	PTH1R	3	A/G	0.022	0.004	0.39	0.022	31.6
rs11719201	b	ADCY5	3	T/C	0.046	0.004	0.23	0.076	109.2
rs10935733		CPA3	3	T/C	0.022	0.004	0.42	0.024	33.0
rs13322435	d	CCNL1-LEKR1	3	A/G	0.053	0.004	0.59	0.136	190.4
rs925098	d	LCORL	4	G/A	0.034	0.004	0.28	0.046	63.6
rs6537307	d	HHIP	4	G/A	0.025	0.004	0.48	0.032	45.0
rs854037		5q11.2	5	A/G	0.027	0.005	0.80	0.022	30.8
rs7729301	d	EBF1	5	A/G	0.024	0.004	0.72	0.023	32.4
rs35261542		CDKAL1	6	C/A	0.044	0.004	0.73	0.078	111.7
rs9379832	c	HIST1H2BE	6	A/G	0.023	0.004	0.71	0.022	30.4
rs7742369	b	HMGA1	6	G/A	0.028	0.005	0.19	0.024	32.4
rs1415701	d	L3MBTL3	6	G/A	0.025	0.004	0.73	0.025	35.4

Table S1: Contiued

SNP			Gene	Chr	ffect/other allele	Beta*	SE	EAF	R^2 (%) **	F-stat ***
rs1101081			ESR1	6	C/T	0.038	0.004	0.73	0.057	79.5
rs798489		d	GNA12	7	C/T	0.023	0.004	0.74	0.021	30.8
rs11765649			IGF2BP3	7	T/C	0.027	0.004	0.76	0.027	37.3
rs6959887	b		TBX20	7	A/G	0.023	0.004	0.61	0.025	35.5
rs138715366	c	d	YKT6-GCK	7	C/T	0.241	0.023	0.99	0.103	136.0
rs62466330			MLXIPL	7	C/T	0.049	0.008	0.07	0.030	42.0
rs13266210			ANK1-NKX6-3	8	A/G	0.031	0.005	0.79	0.031	43.9
rs6989280		d	TRIB1	8	G/A	0.022	0.004	0.70	0.019	26.9
rs12543725		d	SLC45A4	8	G/A	0.023	0.004	0.60	0.026	36.0
rs28510415		d	PTCH1	9	G/A	0.056	0.007	0.09	0.052	70.6
rs2150052	c	d	LPAR1	9	T/A	0.021	0.004	0.50	0.022	31.0
rs7847628	b		PHF19	9	G/A	0.023	0.004	0.67	0.024	32.9
rs700059			STRBP	9	G/A	0.033	0.005	0.16	0.027	37.5
rs61862780			HHEX-IDE	10	T/C	0.028	0.004	0.52	0.039	56.7
rs74233809			NT5C2	10	C/T	0.037	0.007	0.08	0.020	28.7
rs7076938			ADRB1	10	T/C	0.036	0.004	0.73	0.052	74.7
rs2421016		d	PLEKHA1	10	T/C	0.021	0.004	0.48	0.021	30.8
rs72851023	c		INS-IGF2	11	T/C	0.048	0.008	0.07	0.031	41.6
rs10830963	a	d	MTNR1B	11	G/C	0.023	0.004	0.27	0.022	31.2
rs11055034			APOLD1	12	C/A	0.022	0.004	0.73	0.019	27.4
rs139975827	c		ABCC9	12	G/A	0.025	0.004	0.63	0.029	35.7

Table S1: Contiued

SNP			Gene	Chr	ffect/other allele	Beta*	SE	EAF	R^2 (%) **	F-stat ***
rs12823128			ITPR2	12	T/C	0.021	0.004	0.56	0.022	30.8
rs1351394		d	HMGA2	12	T/C	0.044	0.004	0.48	0.095	136.6
rs7964361			IGF1	12	A/G	0.039	0.007	0.08	0.024	33.2
rs2324499	b		LINC00332	13	G/C	0.022	0.004	0.67	0.020	28.6
rs2854355			RB1	13	G/A	0.023	0.004	0.26	0.022	29.7
rs1819436			RNF219-AS1	13	C/T	0.033	0.006	0.87	0.024	34.0
rs12906125	b	d	FES	15	G/A	0.023	0.004	0.69	0.023	32.0
rs7402982	b	d	IGF1R	15	A/G	0.023	0.004	0.42	0.026	36.8
rs1011939	c		GPR139	16	G/A	0.022	0.004	0.31	0.020	28.4
rs113086489		d	CLDN7	17	T/C	0.031	0.004	0.55	0.046	64.8
rs144843919	c		SUZ12P1-CRLF3	17	G/A	0.066	0.012	0.96	0.029	35.7
rs12942207			SP6-SP2	17	C/T	0.022	0.004	0.30	0.021	29.4
rs61154119		d	ACTL9	19	T/G	0.028	0.005	0.84	0.021	27.5
rs10402712	c		PEPD	19	A/G	0.022	0.004	0.27	0.018	24.8
rs6040076	c		JAG1	20	C/G	0.023	0.004	0.51	0.027	37.2
rs28530618	c		C20orf203	20	A/G	0.026	0.004	0.50	0.034	47.1
rs6016377			MAFB	20	T/C	0.024	0.004	0.45	0.028	39.1
rs2229742	a		NRIP1	21	G/C	0.036	0.006	0.87	0.029	42.1
rs134594			KREMEN1	22	C/T	0.023	0.004	0.35	0.023	32.2
rs62240962			SREBF2	22	C/T	0.047	0.007	0.92	0.012	16.3

Chr, chromosome; SNP, single-nucleotide polymorphism; SE, standard error; EAF, effect allele frequency
* per allele effect on birth weight per SD: 1 SD is about 500 gram birth weight.
** explained variance in birth weight (%): $R^2 = 2 \cdot \beta^2 \cdot EAF \cdot (1-EAF)$ [2]

*** calculated as follows: $F = \frac{N-K-1}{K} \bullet \frac{R^2}{1-R^2}$ (where N = sample size, derived from the supplemental data in Horikoshi *et al.*, and K = number of SNPs, e.g. K = 1 if single SNPs are tested) [2]
[a] SNP not available in NEO study (n=2)
[b] SNP not available in CKDgen data, proxy used (n=8), proxies are specified in Supplementary Table 2
[c] SNP not available in CKDgen data and no proxy found (n=11)
[d] SNP excluded in sensitivity analysis, based on statistically significant maternal effects, as reported in the supplemental data in Horikoshi *et al.* (n=20). The threshold for statistical significance was a Bonferroni corrected p-value of 0.0011, based on 45 SNPs.

1. Horikoshi M, Beaumont RN, Day FR, *et al*. Genome-wide associations for birth weight and correlations with adult disease. Nature. 2016;538(7624):248-252.
2. Burgess S, Dudbridge F, Thompson SG. Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods. Stat Med. 2016;35:1880-1906

Table S2: List of used proxies for genetic variants not available in the CKDgen data. Only variants with an R^2>0.80 were selected.

SNP	Proxy	Gene	Chr	Effect/other allele	EAF	R^2
rs3753639	rs905938	ZBTB7B	1	C/T	0.27	0.876
rs11719201	rs11708067	ADCY5	3	G/A	0.20	0.950
rs7742369	rs1776877	HMGA1	6	G/A	0.16	1.000
rs6959887	rs988270*	TBX20	7	C/T	0.68	0.962
rs7847628	rs3933326*	PHF19	9	G/A	0.63	0.895
rs2324499	rs7998537*	LINC00332	13	G/A	0.68	0.962
rs12906125	rs6227	FES	15	C/T	0.63	0.965
rs7402982	rs2017500	IGF1R	15	G/A	0.45	0.935

Chr, chromosome; EAF, effect allele frequency; SNP, single-nucleotide polymorphism
* Removed from analysis because in LD (R^2>0.001) with other SNP.

Table S3: According to four birth weight categories, difference in kidney function, urinary albumin-to-creatinine ratio, risk of CKD, and albuminuria, at age 45-65 years in 6,671 participants of the Netherlands Epidemiology of Obesity study, including only complete cases.

Birth weight (kg)	Crude	Model 1	Model 2	Model 3
		Difference in eGFR		
<2.5	-0.25 (-2.11; 1.61)	-0.04 (-1.81; 1.73)	-0.18 (-1.97; 1.61)	-0.10 (-1.90; 1.70)
2.5 to <3.0	-0.56 (-1.82; 0.70)	-0.38 (-1.61; 0.85)	-0.44 (-1.68; 0.80)	-0.42 (-1.66; 0.81)
3.0 to <4.0 (ref)	0	0	0	0
≥4.0	0.70 (-0.78; 2.18)	0.10 (-1.30; 1.51)	0.19 (-1.21; 1.59)	0.20 (-1.20; 1.59)
		Difference in UACR		
<2.5	-0.16 (-0.34; 0.02)	-0.14 (-0.30; 0.01)	-0.20 (-0.37; 0.03)	-0.20 (-0.37; -0.02)*
2.5 to <3.0	0.09 (-0.29; 0.46)	0.10 (-0.27; 0.46)	0.08 (-0.31; 0.46)	0.09 (-0.30; 0.47)
3.0 to <4.0 (ref)	0	0	0	0
≥4.0	0.34 (-0.42; 1.10)	0.35 (-0.41; 1.12)	0.38 (-0.39; 1.15)	0.36 (-0.41; 1.12)
		Odds ratio for CKD [a]		
<2.5	0.86 (0.29; 2.53)	0.81 (0.26; 2.46)	0.79 (0.26; 2.39)	0.79 (0.26; 2.37)
2.5 to <3.0	0.98 (0.50; 1.94)	1.02 (0.52; 2.02)	1.01 (0.51; 2.01)	1.02 (0.51; 2.02)
3.0 to <4.0 (ref)	1	1	1	1
≥4.0	0.60 (0.25; 1.43)	0.73 (0.31; 1.74)	0.73 (0.31; 1.74)	0.72 (0.30; 1.71)
		Odds ratio for moderately or severely increased albuminuria [b]		
<2.5	1.25 (0.67; 2.32)	1.48 (0.79; 2.78)	1.40 (0.74; 2.64)	1.47 (0.77; 2.79)
2.5 to <3.0	1.08 (0.63; 1.83)	1.19 (0.70; 2.02)	1.17 (0.70; 1.98)	1.17 (0.70; 1.96)
3.0 to <4.0 (ref)	1	1	1	1
≥4.0	0.68 (0.37; 1.26)	0.64 (0.34; 1.21)	0.65 (0.34; 1.24)	0.66 (0.35; 1.26)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio. * p<0.05. Results were based on analyses weighted towards the BMI distribution of the general population. Mean (95%-CI) baseline eGFR in the reference group is 86.5 (85.8; 87.3) mL/min/1.73m^2. Mean (95%-CI) baseline UACR in the reference group is 0.82 (0.66; 0.99) mg/g.

[a] Analyses were weighted towards the BMI distribution of the general population, therefore no absolute numbers were presented. The prevalence of CKD was 2.2%.

[b] Analyses were weighted towards the BMI distribution of the general population, therefore no absolute numbers were presented. The prevalence of albuminuria was 3%.

Model 1: adjusted for age and sex.

Model 2: Model 1, additionally adjusted for race and level of education.

Model 3: Model 2, additionally adjusted for cigarette smoking and alcohol consumption.

Table S4: According to four birth weight categories, difference in kidney function, urinary albumin-to-creatinine ratio, risk of CKD, and albuminuria, at age 45-65 years restricted to Caucasian participants (95% of the cohort) of the Netherlands Epidemiology of Obesity study.

Birth weight (kg)	Crude	Model 1	Model 2	Model 3
		Difference in eGFR		
<2.5	-0.86 (-2.58; 0.86)	-0.06 (-1.67; 1.55)	-0.14 (-1.75; 1.47)	-0.11 (-1.71; 1.50)
2.5 to <3.0	-0.68 (-2.08; 0.72)	-0.08 (-1.37; 1.21)	-0.15 (-1.45; 1.14)	-0.14 (-1.42; 1.13)
3.0 to <4.0 (ref)	0	0	0	0
≥4.0	0.67 (-0.90; 2.24)	0.56 (-0.95; 2.06)	0.57 (-0.92; 2.06)	0.57 (-0.90; 2.05)
		Difference in UACR		
<2.5	-0.03 (-0.57; 0.52)	-0.05 (-0.60; 0.51)	-0.07 (-0.62; 0.48)	-0.07 (-0.62; 0.48)
2.5 to <3.0	-0.01 (-0.34; 0.22)	-0.02 (-0.36; 0.31)	-0.05 (-0.38; 0.28)	-0.04 (-0.37; 0.29)
3.0 to <4.0 (ref)	0	0	0	0
≥4.0	0.28 (-0.35; 0.91)	0.26 (-0.38; 0.91)	0.27 (-0.38; 0.91)	0.25 (-0.39; 0.89)
		Odds ratio for CKD [a]		
<2.5	1.23 (0.47; 3.21)	1.01 (0.38; 2.65)	0.99 (0.37; 2.61)	0.98 (0.37; 2.58)
2.5 to <3.0	1.37 (0.74; 2.53)	1.24 (0.68; 2.26)	1.23 (0.67; 2.25)	1.22 (0.67; 2.22)
3.0 to <4.0 (ref)	1	1	1	1
≥4.0	0.76 (0.34; 1.66)	0.79 (0.36; 1.74)	0.79 (0.36; 1.75)	0.77 (0.35; 1.69)
		Odds ratio for moderately or severely increased albuminuria [b]		
<2.5	1.26 (0.65; 2.44)	1.39 (0.71; 2.73)	1.35 (0.69; 2.64)	1.39 (0.70; 2.73)
2.5 to <3.0	1.11 (0.64; 1.94)	1.17 (0.67; 2.04)	1.13 (0.65; 1.95)	1.13 (0.66; 1.94)
3.0 to <4.0 (ref)	1	1	1	1
≥4.0	0.83 (0.45; 1.54)	0.75 (0.40; 1.40)	0.76 (0.40; 1.42)	0.76 (0.40; 1.43)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio. * p<0.05. Results were based on analyses weighted towards the BMI distribution of the general population. Mean (95%-CI) baseline eGFR in the reference group is 86.5 (85.8; 87.3) mL/min/1.73m^2. Mean (95%-CI) baseline UACR in the reference group is 0.82 (0.66; 0.99) mg/g.

[a] Analyses were weighted towards the BMI distribution of the general population, therefore no absolute numbers were presented. The prevalence of CKD was 2.2%.

[b] Analyses were weighted towards the BMI distribution of the general population, therefore no absolute numbers were presented. The prevalence of albuminuria was 3%.

Model 1: adjusted for age and sex.

Model 2: Model 1, additionally adjusted for race and level of education.

Model 3: Model 2, additionally adjusted for cigarette smoking and alcohol consumption.

Table S5: Proportion of risk factors for CKD according to quartiles of the genetic risk score for birth weight, in participants of the Netherlands Epidemiology of Obesity study.

	Proportion of participants with risk factor for CKD, per quartile of genetic risk score for birth weight			
	Quartile 1 (<2.17)	Quartile 2 (2.17 to 2.26)	Quartile 3 (2.27 to 2.35)	Quartile 4 (≥2.36)
Women	53.8	55.3	57.5	57.2
≥55 years	56.2	58.6	58.6	57.2
Lower education	52.2	52.4	54.2	51.6
BMI ≥30.0 kg/m^2	13.6	16.6	15.7	16.3
Diabetes	6.3	5.9	5.0	4.3

BMI, body mass index; CKD, chronic kidney disease.
Results were based on analyses weighted towards the BMI distribution of the general Dutch population.

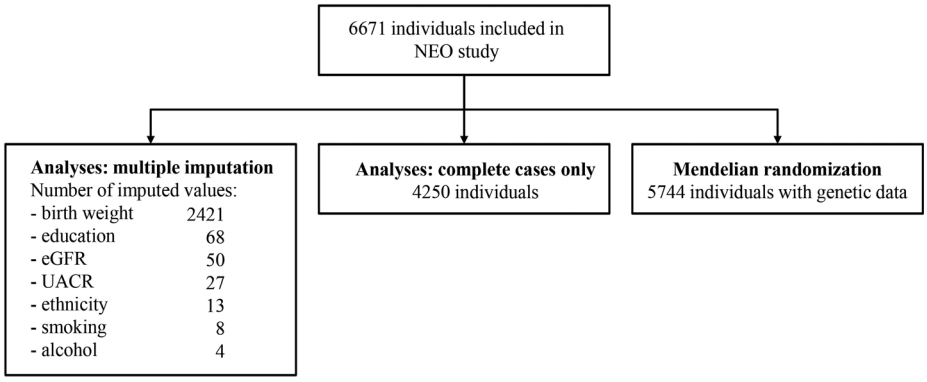

Figure S1: Flow chart of 6,671 participants of the Netherlands Epidemiology of Obesity study.

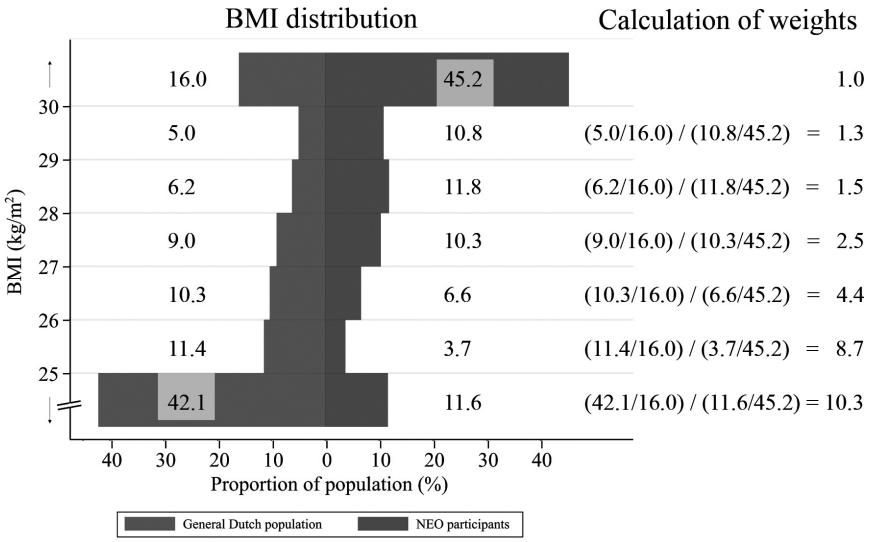

Figure S2: BMI distribution of the NEO participants (blue) compared to the general Dutch population (red), and derivation of the weights for weighted analyses. Owing to the oversampling of overweight individuals, the BMI distribution of NEO participants substantially deviates from the general population. For generalizability purposes, analyses in NEO participants were weighted towards the distribution of the general population. For example, the weight for analysis in NEO participants with a BMI< 25 kg/m² was calculated as follows: in NEO participants the ratio of those with a BMI <25 kg/m² compared to those with a BMI >30 kg/m² was 11.6/45.2=0.257. In the general population this ratio was 42.1/16.0=2.63. The weight for participants of the NEO study with BMI <25 kg/m² was then 2.63/0.257=10.3. In this manner, the BMI distribution of NEO participants (blue) becomes similar to the general population (red).

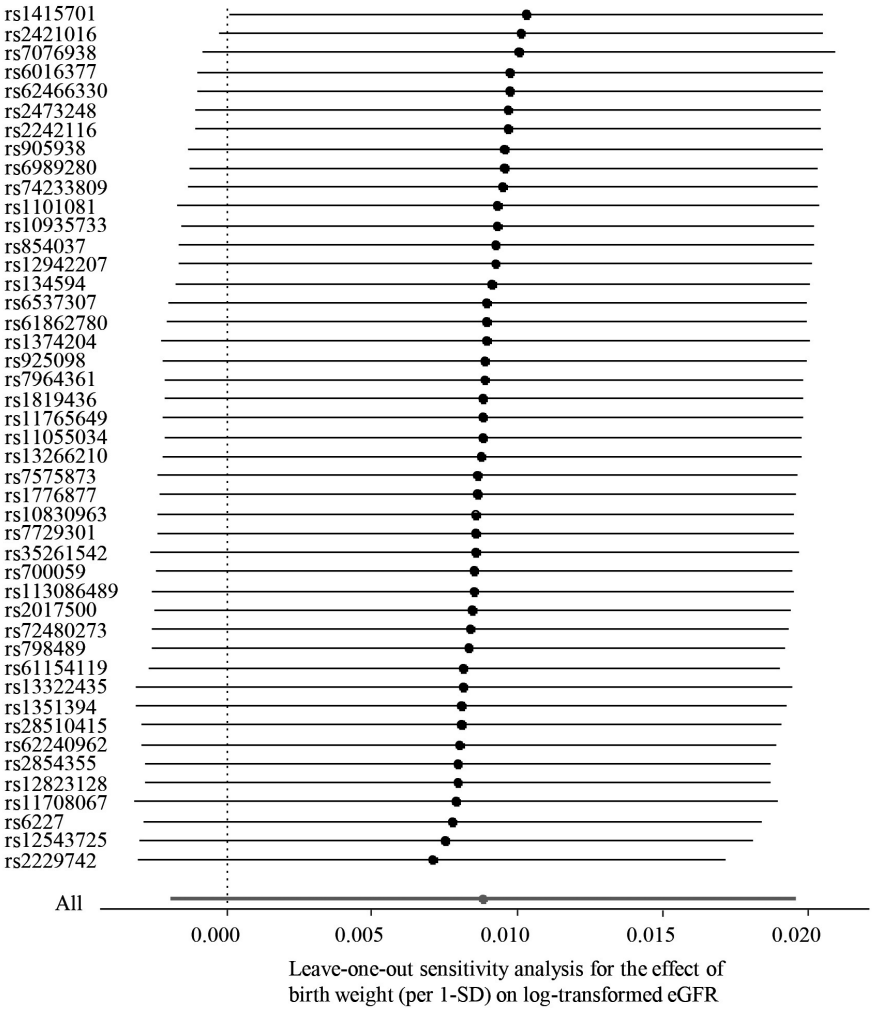

Figure S3: Leave-one-out sensitivity analysis to identify potential influential outliers. For each SNP the summary effect estimate is plotted after excluding a single SNP. In case of influential outliers, leaving the single SNP out, may result in a large deviation of the effect estimate, compared to the overall effect estimate of all SNPs. In the present study, all effect estimates excluding one single SNP are roughly comparable to the overall effect including all SNPs. Therefore, this analysis is not suggestive for pleiotropy owing to outliers.

eGFR, estimated glomerular filtration rate; SD, standard deviation; SNP, single-nucleotide polymorphism.

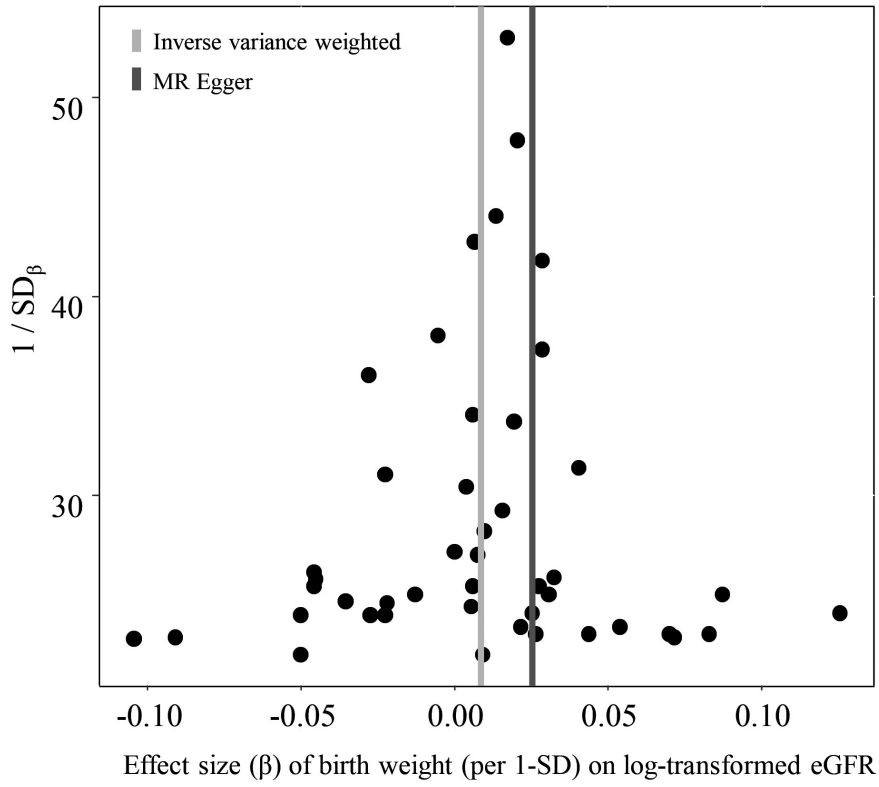

Figure S4: Funnel plot analysis to detect directional pleiotropy. For each SNP, the causal estimate (β) is plotted against the precision of the causal estimate. Asymmetry may arise when certain SNPs have very strong effects on the outcome, which may indicate directional horizontal pleiotropy. In the present study, the funnel plot is symmetrical, which is reflected also by the non-significant MR-Egger intercept test (p=0.37).
eGFR, estimated glomerular filtration rate; SD, standard deviation; SNP, single-nucleotide polymorphism.