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Low birth weight, later renal function, and the roles of adulthood blood pressure, diabetes, and obesity in a British birth cohort

Richard J. Silverwood1, Mary Pierce2, Rebecca Hardy2, Naveed Sattar3, Peter Whincup4, Charles Ferro5, Caroline Savage6, Diana Kuh2 and Dorothea Nitsch1

1Department of Non-Communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK; 2MRC Unit for Lifelong Health and Ageing, University College London, London, UK; 3Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; 4Population Health Research Centre, Division of Population Health Sciences and Education, St George’s, University of London, London, UK; 5Department of Renal Medicine, Queen Elizabeth Hospital, Birmingham, UK and 6School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

Low birth weight has been shown to be associated with later renal function, but it is unclear to what extent this is explained by other established kidney disease risk factors. Here we investigate the roles of diabetes, hypertension, and obesity using data from the Medical Research Council National Survey of Health and Development, a socially stratified sample of 5362 children born in March 1946 in England, Scotland, and Wales, and followed since. The birth weight of 2192 study members with complete data was related to three markers of renal function at age 60–64 (estimated glomerular filtration rate (eGFR) calculated using creatinine and cystatin C (eGFRcys), eGFR calculated using creatinine and cystatin C (eGFRcr-cys), and the urine albumin–creatinine ratio) using linear regression. Each 1 kg lower birth weight was associated with a 2.25 ml/min per 1.73 m² (95% confidence interval 0.80–3.71) lower eGFRcys and a 2.13 ml/min per 1.73 m² (0.69–3.58) lower eGFRcr-cys. There was no evidence of an association with urine albumin–creatinine ratio. These associations with eGFR were not confounded by socioeconomic position and were not explained by diabetes or hypertension, but there was some evidence that they were stronger in study members who were overweight in adulthood. Thus, our findings highlight the role of lower birth weight in renal disease and suggest that in those born with lower birth weight particular emphasis should be placed on avoiding becoming overweight.

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KEYWORDS: birth weight; diabetes; estimated glomerular filtration rate; hypertension; kidney disease; obesity

There is increasing recognition of the importance of early life factors in adult renal disease. A recent meta-analysis has shown that low birth weight is associated with later kidney disease in middle-aged and older populations.1 However, it is, to date, unclear to what extent this association is explained by adverse circumstances of the mother in pregnancy (via programming) or of the child or young adult.

Low birth weight has been found, in many studies, to be associated with later higher blood pressure2–4 and with the development of type 2 diabetes.5,6 Hypertension and diabetes are major risk factors for the development of kidney disease at older ages7,8 and thus may lie on the causal pathway between low birth weight and chronic kidney disease (CKD).

There is mounting evidence that adult obesity increases the risk of kidney disease.9 In addition, some studies have found accelerated childhood weight gain to amplify the association between birth weight and diabetes.10 Obesity thus appears to be important in the interrelation of birth weight, diabetes, and renal disease, being both a risk factor for renal disease in its own right and a modifier of the birth weight–diabetes association.

The possible pathophysiological pathways between birth weight and reduced renal function include intrauterine growth restriction (as evidenced by lower birth weight) leading to a lower nephron number, glomerular hyperfiltration later in life, and subsequent increased risk of CKD. The importance of a lower nephron number has been highlighted in adults with primary hypertension.11

The Medical Research Council National Survey of Health and Development (NSHD) provides a unique opportunity to explore the pathways by which low birth weight is associated with later kidney function. This study is a prospective cohort representative of the British population that has measured birth weight, subsequent anthropometric markers of growth and weight gain, blood pressure during
adulthood, and has documented social circumstances throughout life. Data collected at the age of 60–64 years allow us to assess albuminuria and estimated glomerular filtration rate (eGFR). An additional advantage is that this study has measurements of serum cystatin C as well as serum creatinine, which has been suggested as a superior marker of kidney function, with combined creatinine-cystatin C equations recently found to perform better than equations based on either of these markers alone.\textsuperscript{12} We have previously shown that study members becoming overweight in early adulthood (age 26 or 36 years) were at a greater risk of CKD than those who became overweight later in adulthood.\textsuperscript{13} We hypothesized that any effect of low birth weight on later renal function would be mainly explained by blood pressure and diabetes, and that birth weight-renal function associations would be stronger in overweight adults.

**RESULTS**

Data on one or more of the renal function measures at the age of 60–64 years (eGFR calculated using cystatin C alone (eGFRcys), eGFR calculated using cystatin C in combination with creatinine (eGFRcr-cys), and urine albumin-creatinine ratio (uACR)) were available for 2198 study members; birth weight data were also available for 2192 members. Mean birth weight in the cohort was 3.38 kg (s.d. 0.54), mean eGFRcys was 94.3 ml/min per 1.73 m\(^2\) (s.d. 14.4), mean eGFRcr-cys was 95.2 ml/min per 1.73 m\(^2\) (s.d. 13.3), and median uACR was 0.55 mg/mmol (interquartile range 0.43; Table 1). Using the KDIGO (Kidney Disease: Improving Global Outcomes) definition of CKD as eGFR <60 ml/min per 1.73 m\(^2\),\textsuperscript{14} 35 out of 2052 (1.7%) study members had CKD using eGFRcys and 24 out of 1848 (1.3%) had CKD using eGFRcr-cys.

In childhood, almost 60% of study members were of manual social class, but by the age of 53 years this had Table 1 | Distributions of birth weight, kidney function, and potential confounder or mediator variables in the MRC National Survey of Health and Development

| Variable | N | Males | N | Females | N | Total |
|----------|---|-------|---|---------|---|-------|
| Birth weight (kg) | 2798 | 3.44 (0.56) | 2529 | 3.30 (0.51) | 5327 | 3.38 (0.54) |
| Cystatin C-based eGFR at age 60-64 years (ml/min per 1.73 m\(^2\)) | 996 | 97.0 (14.3) | 1056 | 91.8 (14.1) | 2052 | 94.3 (14.4) |
| Creatinine and cystatin C-based eGFR at age 60-64 years (ml/min per 1.73 m\(^2\)) | 908 | 95.9 (12.7) | 940 | 94.6 (13.8) | 1848 | 95.2 (13.3) |
| Log-urine albumin-creatinine ratio at age 60-64 years (mg/mmol) | 1042 | --0.57 (0.82) | 1131 | --0.42 (0.63) | 2173 | --0.49 (0.73) |
| HbA1c at age 60-64 years (%) | 989 | 5.86 (0.76) | 1056 | 5.84 (0.66) | 2045 | 5.85 (0.71) |
| Systolic blood pressure at age 60-64 years (mm Hg) | 1062 | 137.5 (18.0) | 1147 | 130.5 (17.3) | 2209 | 133.9 (18.0) |
| Diastolic blood pressure at age 60-64 years (mm Hg) | 1062 | 78.3 (9.9) | 1147 | 74.5 (9.6) | 2209 | 76.3 (9.9) |
| Childhood socioeconomic position (age 4 years) | 2355 | | 2145 | | 4500 | |
| I and II | 523 (22.2) | 487 (22.7) | 1010 (22.4) |
| III Nonmanual | 432 (18.3) | 392 (18.3) | 824 (18.3) |
| III Manual | 732 (31.1) | 689 (32.1) | 1421 (31.6) |
| IV and V | 668 (28.4) | 577 (26.9) | 1245 (27.7) |
| Adulthood socioeconomic position (age 53 years) | 1418 | | 1463 | | 2881 | |
| I and II | 836 (59.0) | 824 (56.3) | 1660 (57.6) |
| III Nonmanual | 266 (18.8) | 346 (23.7) | 612 (21.2) |
| III Manual | 232 (16.4) | 161 (11.0) | 393 (13.6) |
| IV and V | 84 (5.9) | 132 (9.0) | 216 (7.5) |
| Self-reported diabetes by age 60-64 years | 1180 | | 1273 | | 2453 | |
| No | 1079 (91.4) | 1191 (93.6) | 2270 (92.5) |
| Yes | 101 (8.6) | 82 (6.4) | 183 (7.5) |
| On diabetes treatment at age 60-64 years | 1268 | | 1358 | | 2626 | |
| No | 1182 (93.2) | 1301 (95.8) | 2483 (94.6) |
| Yes | 86 (6.8) | 57 (4.2) | 143 (5.4) |
| Midlife systolic blood pressure trajectory\textsuperscript{b} | 1840 | | 1819 | | 3659 | |
| Normal | 1736 (94.3) | 1687 (92.7) | 3423 (93.6) |
| Increaser/high | 104 (5.7) | 132 (7.3) | 236 (6.4) |
| On hypertension treatment at age 60-64 years | 1268 | | 1358 | | 2626 | |
| No | 862 (68.0) | 985 (72.5) | 1847 (70.3) |
| Yes | 406 (32.0) | 373 (27.5) | 779 (29.7) |
| Overweight at age 36 years | 1632 | | 1648 | | 3280 | |
| No | 913 (55.9) | 1221 (74.1) | 2134 (65.1) |
| Yes | 719 (44.1) | 427 (25.9) | 1146 (34.9) |

Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MRC, Medical Research Council.

\textsuperscript{a}HbA1c (mmol/mol) = (HbA1c (%) – 2.13) × 10.929.

\textsuperscript{b}Latent trajectories previously derived from systolic blood pressure data at ages 36, 43, and 53 years.\textsuperscript{15}
reduced to 21%. Over 6% of the study members were in the increaser or high midlife systolic blood pressure (SBP) latent trajectory (previously derived from SBP data at ages 36, 43, and 53 years). By the age of 60–64 years, 7% of the study members reported being diagnosed with diabetes, 5% were on diabetes treatment, and 30% were on antihypertensive treatment. Mean glycated hemoglobin (HbA1c) was 5.8% (s.d. 0.7; 40.4 mmol/mol (s.d. 7.7)), mean SBP was 134 mm Hg (s.d. 18), and mean diastolic blood pressure (DBP) was 76.3 mm Hg (s.d. 9.9). In all, 44% of men and 26% of women were overweight at the age of 36 years.

The distributions of the three renal outcome variables (eGFR, eGFRcr-cys, and log-uACR), HbA1c, SBP, and DBP were examined by quartiles of birth weight for men and women (Supplementary Information and Supplementary Table S1 online). There were clear trends of higher eGFR and lower log-uACR, HbA1c, and SBP with higher birth weight, although these varied somewhat by sex.

Associations between birth weight and each renal outcome, potential confounder (childhood socioeconomic position (SEP)), and potential mediator (adulthood SEP, overweight at the age of 36 years, self-reported diabetes by the age of 60–64 years, on diabetes treatment at the age of 60–64 years, HbA1c at the age of 60–64 years, midlife SBP trajectory, on antihypertensive treatment at the age of 60–64 years, DBP at the age of 60–64 years, and 53 years). By the age of 60–64 years, 7% of the study members were associated with birth weight. Each 1 kg lower birth weight was associated with 2.02 ml/min per 1.73 m² (95% confidence interval (CI) 0.79–3.25) lower eGFR, 1.88 ml/min per 1.73 m² (95% CI 0.66–3.11) lower eGFRcr-cys, and 0.055 log-μg/mmol (95% CI –0.007 to 0.118) higher log-uACR. Lower birth weight increased the odds of diabetes by both self-report and treatment, and was somewhat associated with higher HbA1c at the age of 60–64 years. Lower birth weight was also associated with being in the increaser/high midlife SBP trajectory and being on antihypertensive treatment, as well as with higher SBP at the age of 60–64 years, but not with DBP. Those with lower birth weight also had lower odds of being overweight at the age of 36 years.

Associations between each potentially confounding or mediating variable and each renal outcome were examined using linear regression and all available data (Table 3). There was evidence that childhood SEP was associated with renal function, with more manual occupations associated with lower eGFR and higher log-uACR. Stronger trends were seen for adulthood SEP with both eGFR measures, but not with log-uACR. All three indicators of diabetes/dysglycemia were only weakly associated with lower eGFR, but strongly

| Table 2 | Bivariate regression models for a 1-kg increase in birth weight |
|---------|----------------------|------------------|------------------|------------------|
| Outcome                                    | N    | Coeff | 95% CI          | P overall |
| Cystatin C-based eGFR at age 60-64 years (ml/min per 1.73 m²) | 2046 | 2.02  | 0.79 to 3.25    | 0.001   |
| Creatinine and cystatin C-based eGFR at age 60-64 years (ml/min per 1.73 m²) | 1842 | 1.88  | 0.66 to 3.11    | 0.003   |
| Log-urine albumin-creatinine ratio at age 60-64 years (mg/mmol) | 2167 | –0.055 | –0.118 to 0.007 | 0.08    |
| HbA1c at age 60-64 years (%) | 2024 | 0.060 | –0.123 to 0.003 | 0.06     |
| Systolic blood pressure at age 60-64 years (mm Hg) | 2169 | 2.22  | 3.72 to –0.72   | 0.004    |
| Diastolic blood pressure at age 60-64 years (mm Hg) | 2169 | –0.18 | –1.01 to 0.65   | 0.67     |
| Outcome                                    | N    | Coeff | 95% CI          | P overall |
| Childhood socioeconomic position (age 4 years) | 2030 | 0.18  | 2.22 to 0.06    | 0.04     |
| I and II (Ref)                             |      |      |                 |          |
| III Nonmanual                              | 0.75 | 0.57 to 0.97  |          |
| III Manual                                 | 0.86 | 0.68 to 1.09  |          |
| IV and V                                   | 0.71 | 0.56 to 0.91  |          |
| Adulthood socioeconomic position (age 53 years) | 2050 | 0.90  | 1.40 to 0.50    | 0.04     |
| I and II (Ref)                             |      |      |                 |          |
| III Nonmanual                              | 1.12 | 0.90 to 1.40  |          |
| III Manual                                 | 0.85 | 0.64 to 1.13  |          |
| IV and V                                   | 1.14 | 0.78 to 1.66  |          |
| Self-reported diabetes by age 60-64 years (yes vs. no) | 1998 | 0.66  | 0.46 to 0.94    | 0.02     |
| On diabetes treatment at age 60-64 years (yes vs. no) | 2192 | 0.50  | 0.34 to 0.74    | 0.001    |
| Midlife systolic blood pressure trajectory (increaser/high vs. normal) | 2173 | 0.71  | 0.50 to 1.02    | 0.07     |
| On hypertension treatment at age 60-64 years (yes vs. no) | 2192 | 0.79  | 0.66 to 0.96    | 0.01     |
| Overweight at age 36 years (yes vs. no)     | 1994 | 1.35  | 1.12 to 1.64    | 0.002    |

Abbreviations: CI, confidence interval; Coeff, coefficient; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; OR, odds ratio; Ref, reference.

Restricted to study members non-missing for at least one measure of renal function at the age of 60–64 years.

All models adjusted for sex. Models with outcomes at the age of 60–64 years additionally adjusted for age at measurement.

*Likelihood ratio test.

Linear regression.

Coef with HbA1c (mmol/mol) as outcome = Coef with HbA1c (%) as outcome × 10.929.

Multinomial logistic regression.

Logistic regression.

Latent trajectories previously derived from systolic blood pressure data at ages 36, 43, and 53 years.15
associated with higher log-uACR. Being in the increaser/high midlife SBP trajectory or on antihypertensive treatment was associated with lower eGFR and higher log-uACR, although higher SBP at the age of 60–64 years was only associated with higher log-uACR. Being overweight at the age of 36 years was strongly associated with lower eGFR and higher log-uACR.

To better understand by which pathways low birth weight was associated with renal function, subsequent analyses sequentially adjusted associations between birth weight and each outcome using study members with complete data on all variables (Table 4). For both measures of eGFR, adjustment for childhood and adulthood SEP attenuated the minimally adjusted associations with birth weight to a very small extent (model 2; from 2.25 (95% CI 0.80–3.71) and 2.13 (95% CI 0.69–3.58) ml/min per 1.73 m² for higher birth weight to 2.19 (95% CI 0.73–3.64) and 2.09 (95% CI 0.65–3.54) ml/min per 1.73 m² for eGFRcys and eGFRcys-cys, respectively). Further adjustment for diabetes (model 3) had a greater effect (to 2.05 (95% CI 0.60–3.50) and 1.97 (95% CI 0.52–3.42) ml/min per 1.73 m²), as did adjustment for hypertension (model 4; to 2.07 (95% CI 0.62–3.51) and 2.01 (95% CI 0.57–3.46) ml/min per 1.73 m²). Adjustment for overweight at the age of 36 years (model 5) amplified the associations somewhat (to 2.41 (95% CI 0.96–3.86) and 2.31 (95% CI 0.86–3.76) ml/min per 1.73 m²). The fully adjusted models (model 6) thus showed

Table 4 | Bivariate linear regression models for associations with renal function at the age of 60–64 years

| Outcome | Explanatory variable | N    | Coeff  | 95% CI         | P overall* | P trend* |
|---------|----------------------|------|--------|----------------|------------|----------|
| Cystatin C-based eGFR at age 60–64 years (ml/min per 1.73 m²) | Childhood socioeconomic position (age 4 years) | 1898 | 0.003  | 0.001          |            |          |
|         | I and II             | (Ref) |        |                |            |          |
|         | III Nonmanual        | 0.07  | –1.80  | 1.95           |            |          |
|         | III Manual           | –2.55 | –4.26  | 0.84           |            |          |
|         | IV and V             | 2.20  | –3.97  | 0.42           |            |          |
|         | Adulthood socioeconomic position (age 53 years) | 1917 |       |                | <0.001     | <0.001   |
|         | I and II             | (Ref) |        |                |            |          |
|         | III Nonmanual        | –2.44 | –4.00  | 0.88           |            |          |
|         | III Manual           | –3.14 | –5.21  | 1.08           |            |          |
|         | IV and V             | –3.19 | –5.96  | 0.52           |            |          |
|         | Self-reported diabetes by age 60–64 years (yes vs. no) | 1871 |       |                | 0.02       |          |
|         | On diabetes treatment at age 60–64 years (yes vs. no) | 2006 |       |                | 0.04       |          |
|         | HbA1c at age 60–64 years (per %)² | 1964 |       |                | 0.09       |          |
|         | Midlife systolic blood pressure trajectory (increaser/high vs. normal)² | 2027 |       |                | 0.01       |          |
|         | On hypertension treatment at age 60–64 years (yes vs. no) | 2046 |       |                | <0.001     |          |
|         | Systolic blood pressure at the age of 60–64 years (per 20 mm Hgd)² | 2027 |       |                | 0.18       |          |
|         | Diastolic blood pressure at age 60–64 years (per 10 mm Hgd)² | 2027 |       |                | 0.03       |          |
|         | Overweight at age 36 years (yes vs. no) | 1863 |       |                | <0.001     |          |
|         | Childhood socioeconomic position (age 4 years) | 1708 |       |                | 0.30       | 0.13     |
|         | (Ref)                |        |        |                |            |          |
|         | III Nonmanual        | 0.20  | –1.64  | 2.04           |            |          |
|         | III Manual           | –1.24 | 2.92   | 0.45           |            |          |
|         | IV and V             | –0.97 | –2.74  | 0.80           |            |          |
|         | Adulthood socioeconomic position (age 53 years) | 1739 |       |                | 0.01       | 0.001    |
|         | I and II             | (Ref) |        |                |            |          |
|         | III Nonmanual        | –1.86 | –3.42  | 0.29           |            |          |
|         | III Manual           | –2.15 | –4.27  | 0.02           |            |          |
|         | IV and V             | –3.06 | –5.76  | 0.37           |            |          |
|         | Self-reported diabetes by age 60–64 years (yes vs. no) | 1689 |       |                | 0.11       |          |
|         | On diabetes treatment at age 60–64 years (yes vs. no) | 1842 |       |                | 0.04       |          |
|         | HbA1c at age 60–64 years (per %)² | 1768 |       |                | 0.007      |          |
|         | Midlife systolic blood pressure trajectory (increaser/high vs. normal)² | 1825 |       |                | 0.02       |          |
|         | On hypertension treatment at age 60–64 years (yes vs. no) | 1842 |       |                | <0.001     |          |
|         | Systolic blood pressure at age 60–64 years (per 20 mm Hgd)² | 1826 |       |                | 0.28       |          |
|         | Diastolic blood pressure at age 60–64 years (per 10 mm Hgd)² | 1826 |       |                | 0.28       |          |
|         | Overweight at age 36 years (yes vs. no) | 1676 |       |                | <0.001     |          |
|         | Childhood socioeconomic position (age 4 years) | 2006 |       |                | 0.09       | 0.01     |
|         | (Ref)                |        |        |                |            |          |
|         | III Nonmanual        | 0.021 | –0.074 | 0.117          |            |          |
|         | III Manual           | 0.081 | –0.006 | 0.167          |            |          |
|         | IV and V             | 0.101 | 0.011  | 0.191          |            |          |
|         | Adulthood socioeconomic position (age 53 years) | 2027 |       |                | 0.15       | 0.32     |
|         | I and II             | (Ref) |        |                |            |          |
|         | III Nonmanual        | 0.010 | –0.070 | 0.090          |            |          |
|         | III Manual           | 0.018 | 0.013  | 0.223          |            |          |
|         | IV and V             | 0.030 | 0.167  | 0.107          |            |          |
|         | Self-reported diabetes by age 60–64 years (yes vs. no) | 1974 |       |                | <0.001     |          |
|         | On diabetes treatment at age 60–64 years (yes vs. no) | 2167 |       |                | <0.001     |          |
|         | HbA1c at age 60–64 years (per %)² | 2001 |       |                | <0.001     |          |
|         | Midlife systolic blood pressure trajectory (increaser/high vs. normal)² | 2149 |       |                | <0.001     |          |
|         | On hypertension treatment at age 60–64 years (yes vs. no) | 2167 |       |                | <0.001     |          |
|         | Systolic blood pressure at age 60–64 years (per 20 mm Hgd)² | 2144 |       |                | <0.001     |          |
|         | Diastolic blood pressure at age 60–64 years (per 10 mm Hgd)² | 2144 |       |                | <0.001     |          |
|         | Overweight at age 36 years (yes vs. no) | 1971 |       |                | 0.140      | 0.069    |

Abbreviations: CI, confidence interval; Coeff, coefficient; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; Ref, reference. Restricted to study members nonmissing for birth weight. All models adjusted for sex and age at renal function measurement.

*Likelihood ratio test.
²HbA1c (mmol/mol) coeff = HbA1c (%) coeff/10.29.
²Latent trajectories previously derived from systolic blood pressure data at ages 36, 43, and 53 years.¹⁵
²Approximately 1 s.d.
Table 5 | Linear regression models for a 1-kg increase in birth weight by overweight status at the age of 36 years

| Outcome                                      | Overweight at age 36 years | N  | Coeff | 95% CI     | P*   |
|----------------------------------------------|---------------------------|----|-------|------------|------|
| Cystatin C-based eGFR (ml/min per 1.73 m²)   | No                        | 1076 | 1.79  | 0.17 to 3.41 | 0.03 |
|                                              | Yes                       | 495  | 3.14  | 0.47 to 5.82 | 0.02 |
| Creatinine and cystatin C-based eGFR (ml/min per 1.73 m²) | No                        | 979  | 1.03  | −0.59 to 2.65 | 0.21 |
|                                              | Yes                       | 445  | 4.03  | 1.34 to 6.71 | 0.003 |
| Log-urine albumin-creatinine ratio (mg/mmol) | No                        | 1088 | 0.017 | −0.062 to 0.096 | 0.68 |
|                                              | Yes                       | 504  | −0.042 | −0.192 to 0.108 | 0.58 |

Abbreviations: CI, confidence interval; Coeff, coefficient; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

Restricted to study members nonmissing for childhood and adulthood socioeconomic status, self-reported diabetes by the age of 60–64 years, on diabetes treatment at the age of 60–64 years, midlife systolic blood pressure trajectory, on hypertension treatment at the age of 60–64 years, and systolic blood pressure at the age of 60–64 years.

Models adjusted for sex, age at renal function measurement, childhood and adulthood socioeconomic position, self-reported diabetes by the age of 60–64 years, on diabetes treatment at the age of 60–64 years, midlife systolic blood pressure trajectory, on hypertension treatment at the age of 60–64 years, systolic blood pressure at the age of 60–64 years, and diastolic blood pressure at the age of 60–64 years.

Wald test for effect modification by overweight status at the age of 36 years: P = 0.08 for cystatin C-based eGFR; P = 0.01 for creatinine and cystatin C-based eGFR. P = 0.31 for log-urine albumin-creatinine ratio.

*Likelihood ratio test.

similar associations between birth weight and eGFR to the minimally adjusted models (2.24 (95% CI 0.80–3.69) and 2.15 (95% CI 0.71–3.60) ml/min per 1.73 m²). Among study members with complete data on all variables, there was no evidence of an association between birth weight and log-uACR (−0.019 (95% CI −0.094 to 0.056) ml/min per kg higher birth weight). Adjustment for SEP, diabetes, and hypertension attenuated this effect even further toward zero.

Fully adjusted models stratified by overweight status at the age of 36 years are presented in Table 5. In study members who were overweight at the age of 36 years, the association between birth weight and eGFR was much stronger than in those who were not overweight (3.14 (95% CI 0.47–8.82) vs. 1.79 (95% CI 0.17–3.41) ml/min per 1.73 m² per 1 kg higher birth weight for eGFRcys and 4.03 (95% CI 1.34–6.71) vs. 1.03 (95% CI −0.59 to 2.65) ml/min per 1.73 m² for eGFRcr-cys). Evidence for this effect modification was stronger for eGFRcr-cys (P = 0.01 by Wald test) than for cystatin C based (P = 0.08). However, there was little evidence of effect modification by overweight at the age of 36 years when considering log-uACR (P = 0.31). Similar results were obtained for effect modification by overweight at ages 43 and 53 years (not shown).

The subset of study members with complete data are likely to be a more health-conscious subgroup who have adhered to follow-up for over 60 years, and thus potentially unrepresentative of the cohort as a whole. An analysis of only complete cases may therefore provide biased results. We used multiple imputation (MI)16,17 to explore the robustness of the complete case results to this potential bias (for full details...
see the Materials and Methods section). The entire analysis was repeated using MI, with the results being very similar to those obtained in the complete case analysis overall (Supplementary Information and Supplementary Tables S2–S5 online). The associations between birth weight and eGFR were slightly weaker in the MI analysis, and that with log-uACR was markedly stronger (although there was little evidence for this association under either approach once diabetes and/or hypertension were adjusted for). Conclusions in both analyses were identical.

**DISCUSSION**

In this large, population-based, prospective study, we found lower birth weight to be associated with eGFR, although not with uACR, measured over 60 years later. The associations with eGFR were not confounded by SEP and were not explained by diabetes or hypertension. There was some evidence that the associations were stronger in study members who were overweight in adulthood.

A recent systematic review and meta-analysis found low birth weight to be associated with later kidney disease in middle-aged and older populations.1 Although the estimated associations in the present analysis are not directly comparable with the meta-analysis as the latter used dichotomous classifications of both birth weight and CKD, the results are clearly in the same direction. White et al.1 suggested that further studies should consider important confounders, such as socioeconomic factors. In the present study, we did not find SEP to be a strong confounder of the birth weight–renal function association.

Low birth weight has been found in many studies to be associated with later blood pressure2–4 and with the development of type 2 diabetes.5,6 Associations between birth weight and self-reported diabetes by the age of 60–64 years, being on diabetes treatment at the age of 60–64 years, midlife SBP trajectory, and being on antihypertensive treatment at the age of 60–64 years were found in this study. Associations with HbA1c and SBP at the age of 60–64 years were weaker but in the expected direction.

Hypertension, diabetes (especially longer duration of diabetes), and adulthood overweight are all acknowledged risk factors for the development of kidney disease at older ages, and thus may lie on the causal pathway between birth weight and CKD.7–9 However, lower birth weight is associated with lower adulthood weight.18 Hence, although people with lower birth weight are at a higher risk of hypertension and diabetes (and thus CKD), this is, to a greater or lesser extent, counterbalanced by adulthood overweight (and the corresponding increased risk of CKD) being less frequent in those with lower birth weight.

To better understand the mechanisms by which low birth weight is associated with renal function, it would be important to distinguish between two causes of low birth weight: (1) preterm birth and (2) intrauterine growth restriction.19,20 This study did not collect data on gestational age, and thus does not allow us to disentangle whether the associations found are related to prematurity or intrauterine growth restriction. However, survival rates among preterm births would have been low in the 1940s, and thus it is likely that most of the variation in birth weights was due to (relative) intrauterine growth restriction. Animal models suggest that prematurity is associated with abnormal glomeruli,21 and that early timing of intrauterine growth restriction leads to reduced nephron number.22 These observations, together with our data, lead us to speculate whether a prolonged increased filtration load in overweight individuals (over several decades of overweight) could lead to a faster decline of kidney function with age, through faster sclerosis of abnormal and/or fewer glomeruli. Autopsy studies in humans would be consistent with such a speculation.23 In children with proteinuric kidney disease, obesity together with lower-term birth amplifies progression of the existing kidney disease, which would fit to our finding for the general population.24

Although we found strong evidence of an association between birth weight and GFR, the evidence of an association between birth weight and albuminuria was much weaker. We suggest that this may be because those with low birth weight who had albuminuria have already decreased their renal function and/or got blood pressure treatment by the time of follow-up. However, we cannot prove this in this study, as we do not have the necessary historical data.

We estimated a 1-kg difference in birth weight to be associated with a > 2 ml/min per 1.73 m² difference in eGFR. Although this effect seems small at an individual level, such a difference in eGFR across a population would decrease the burden of CKD considerably. Such a difference, and the associated implications on CVD risk, would be felt particularly keenly in low- to middle-income countries where a high prevalence of low birth weight is now often followed by rapid growth, leading to overweight in adult life.

A significant strength of this study is that all data were collected prospectively using standardized protocols over 60–64 years. We were able to adjust for all the major potential confounding or mediating factors, although we acknowledge that for some of these a degree of residual confounding may be present. In particular, adjustment for SEP at only two ages may not be sufficient to fully account for the effect of SEP (and associated adverse circumstances) over the life course. There may, in addition, be residual confounding by parental factors for which data were not available, including kidney disease, diabetes mellitus, preeclampsia, hypertension, and smoking.

The availability of multiple measures of renal function (eGFRcys, eGFRcr-cys, and uACR) facilitated a thorough analysis, although the lack of repeated measurements of these measures, as required under the recommended definition of CKD,14 meant that our outcome measures were susceptible to relatively greater measurement error. However, we believe that any outcome measurement error would be independent of birth weight, and thus this should not lead to bias in the results.

The cohort members remaining in the NSHD have been found to be broadly representative of native-born adults
living in England, Scotland, and Wales at the time of data collection at the age of 53 years and at the age of 60–64 years. Hence, we are confident that our analysis sample retains the representativeness of the study population as a whole. The NSHD study population is, however, all white, and therefore our findings cannot be extrapolated to the non-white British population. In addition, the NSHD is a relatively healthy cohort in terms of CKD prevalence, and thus it is unclear whether our findings would extrapolate to other settings. Further studies in such settings are required.

The use of MI allowed us to investigate the role of incomplete follow-up on the results. Although there were some differences between specific MI and complete case models, results were very similar overall and led to identical conclusions. MI analyses rest on the untestable assumption of data being 'missing at random,' but we believe that we included sufficient variables in our imputation model that are predictive of missing values or the processes causing missingness to make this assumption plausible.

In conclusion, we have found lower birth weight to be associated with reduced kidney function over 60 years later, particularly in those who become overweight by early adulthood. This association was not confounded by SEP and was not explained by diabetes or SBP. In those born with low birth weight, particular emphasis should be placed on avoiding the deleterious effects of becoming overweight.

**MATERIALS AND METHODS**

**Participants**

The Medical Research Council (MRC) NSHD is a socially stratified sample of 5362 singleton children born in 1 week in March 1946 in England, Scotland, and Wales, who have been followed up many times since birth. Between October 2006 and February 2011 (at 60–64 years), 2856 eligible study members (those known to be alive and with a known address in England, Scotland, or Wales) were invited for an assessment at one of six Clinical Research Facilities. Of those invited, 2229 (78.0%) were assessed: 1690 (59.1%) attended a clinic examination carried out in their own home by a trained nurse. Of those who had died (n = 778), were living abroad (n = 570), had previously withdrawn from the study (n = 594), or had been lost to follow-up (n = 564). If study members were unable or unwilling to come to one of the Clinical Research Facilities, they were offered a slightly less comprehensive examination carried out in their own home by a trained nurse. Of those invited, 2229 (78.0%) were assessed: 1690 (59.1%) attended a clinic and 539 (18.9%) had a home visit.

**Measures**

At the clinic or home visit at the age of 60–64 years, blood and urine samples were taken and processed according to standardized protocols. Serum creatinine was measured by means of a kinetic version of the Jaffe method using a Siemens Dimension Xpand analyzer at the MRC Human Nutrition Research laboratory in Cambridge. Cystatin C was measured by an automated particle enhanced immunoturbidimetric assay at the Glasgow Royal Infirmary, Department of Clinical Biochemistry. Urine creatinine was measured using a kinetic version of the Jaffe method on a Siemens Dimension analyzer, and urinary albumin was measured by an immunoturbidimetric method on a Siemens BNII/ProSpec analyzer at the MRC Human Nutrition Research laboratory in Cambridge.

eGFR was calculated using two approaches: (1) using cystatin C alone and (2) using cystatin C in combination with creatinine, both using the formulae of Inker et al. These formulae, particularly the combined creatinine and cystatin C version, have been found to perform better than those previously derived. uACR was calculated with adjustment for storage time. log-uACR was used in all analyses owing to the skewed distribution of uACR.

Birth weight of study members, to the nearest quarter of a pound, was extracted from medical records within a few weeks of delivery and converted into kg.

Childhood SEP was derived from the father’s reported occupation when the study participant was aged 4; adulthood SEP was defined as the highest occupational class derived from the study participant’s and their spouse’s reported occupations at the age of 53 years. SEP classification was based on the British Registrar General’s Social Classification: ‘I and II professional and managerial,’ ‘III non-manual,’ ‘III manual skilled,’ or ‘IV and V manual semi or unskilled.’

Adult heights and weights were measured at the ages of 36, 43 and 53 years. Body mass index, defined as weight (kg)/height (m)², was calculated at each age, with a binary variable indicating overweight derived at each age using the standard cut point of 25 kg/m².

Diabetes (self-reported doctor-diagnosed diabetes by the age of 60–64 years, being on diabetes treatment at the age of 60–64 years, and HbA1c level at the age of 60–64 years) and hypertension (previously derived SBP latent trajectory between ages 36 and 53 years, being on antihypertensive treatment at the age of 60–64 years, and measured SBP at the age of 60–64 years) were considered as mediating factors. HbA1c was analyzed using a Tosoh (Tokyo, Japan) G7 analyzer at Addenbrooke’s Hospital in Cambridge. Two measures of SBP at the age of 60–64 years were taken with an Omron 705 (Kyoto, Japan) with the participant seated, with the minimum reading used in this analysis. The remaining diabetes and hypertension data were derived from questionnaire responses.

**Statistical analyses**

Associations between birth weight and each renal outcome (eGFRcys, eGFRcys, and log-uACR) and between birth weight and each potential confounder/mediator (childhood and adulthood SEP, diabetes, hypertension, and overweight at the age of 36 years) were examined using linear, logistic, or multinomial logistic regression as appropriate. All models were adjusted for sex, and those with outcomes at the age of 60–64 years were additionally adjusted for age at measurement.

Associations between each potential confounding/mediating variable and each renal outcome were then examined using linear regression, with all models adjusted for sex and age at renal function measurement.

Next, using study members with complete data on all variables, associations between birth weight and each renal outcome were sequentially adjusted for potential confounding/mediating factors as follows:

**Model 1**: minimally adjusted for sex and age at renal function measurement;

**Model 2**: model 1 + childhood and adulthood SEP;

**Model 3**: model 2 + self-reported diabetes by the age of 60–64 years + on diabetes treatment at the age of 60–64 years + HbA1c at the age of 60–64 years;
Model 4: model 2 + midlife systolic blood pressure trajectory + on antihypertensive treatment at the age of 60–64 years + systolic blood pressure at the age of 60–64 years.

Model 5: model 2 + overweight at the age of 36 years;

Model 6: model 2 + self-reported diabetes by the age of 60–64 years + on diabetes treatment at the age of 60–64 years + HbA1c at the age of 60–64 years + midlife systolic blood pressure trajectory + on antihypertensive treatment at the age of 60–64 years + systolic blood pressure at the age of 60–64 years + overweight at the age of 36 years.

Finally, we tested for effect modification by overweight at the age of 36 years in the fully adjusted model and present results within each strata of overweight at the age of 36 years separately. This analysis was repeated to explore effect modification by overweight at ages 43 and 53 years.

To investigate the potential bias caused by missing data, the entire analysis was repeated using an MI approach. MI allows for uncertainty about missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them. In addition to all the variables included in the analysis models, the imputation model also included occupation at other ages in adulthood, further repeated measures of body mass index in childhood and adulthood, repeated measures of adulthood waist–hip ratio, achieved educational levels of the study member and their parents, and response for data collection at the age of 60–64 years (for example, clinic/home visit, temporary/permanent refusal, untraced). Interactions with sex were included in the imputation model for all variables, as well as interactions between birth weight and body mass index at each age. Study members who were known to have died before or during data collection at the age of 60–64 years were excluded from the MI analysis. A total of 50 imputed data sets were obtained via chained equations.

In all models, potential nonlinear effects of the main explanatory variable were examined by the addition of a quadratic term. Such nonlinear associations were never observed, and thus linear models are presented through.

Strong interactions between sex and other explanatory variables were not found in any of the models, and thus combined male and female models are presented throughout.

The analysis was performed using Stata 12 (Stata statistical software, release 12; StatateCorp, College Station, TX, 2011).

DISCLOSURE
All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL
Table S1. Distributions of kidney function variables, HbA1c, and systolic blood pressure at the age of 60–64 years by birth weight quartile.

Table S2. Bivariate regression models for a 1 kg increase in birth weight in the multiple imputation analysis (n=4584).

Table S3. Bivariate regression linear regression models for associations with renal function at age 60-64 in the multiple imputation analysis (n=4584).

Table S4. Linear regression models for a 1 kg increase in birth weight in the multiple imputation analysis (n=4584).

Table S5. Linear regression models for a 1 kg increase in birth weight by overweight status at age 36 in the multiple imputation analysis (n=4584).

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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