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Early-Life Overweight Trajectory and CKD in the 1946 British Birth Cohort Study

Richard J. Silverwood, PhD,1 Mary Pierce, MD,2 Rebecca Hardy, PhD,2 Claudia Thomas, PhD,3 Charles Ferro, MD,4 Caroline Savage, FMedSci,5 Naveed Sattar, FRCP (Glas), PhD,6 Diana Kuh, PhD,2 and Dorothea Nitsch, MD, MSc,1 on behalf of the National Survey of Health and Development Scientific and Data Collection Teams

Background: Few studies have examined the impact of childhood obesity on later kidney disease, and consequently, our understanding is very limited.

Study Design: Longitudinal population-based cohort.

Setting & Participants: The Medical Research Council National Survey of Health and Development, a socially stratified sample of 5,362 singletons born in 1 week in March 1946 in England, Scotland, and Wales, of which 4,340 were analyzed.

Predictor: Early-life overweight latent classes (never, prepubertal only, pubertal onset, or always), derived from repeated measurements of body mass index between ages 2 and 20 years.

Outcomes & Measurements: The primary outcome was chronic kidney disease (CKD), defined as creatinine- or cystatin C–based estimated glomerular filtration rate (eGFRcr and eGFRcys, respectively) <60 mL/min/1.73 m² or urine albumin-creatinine ratio (UACR) ≥3.5 mg/mmol measured at age 60-64 years. Associations were explored through regression analysis, with adjustment for socioeconomic position, smoking, physical activity level, diabetes, hypertension, and overweight at ages 36 and 53 years.

Results: 2.3% of study participants had eGFRcr <60 mL/min/1.73 m², 1.7% had eGFRcys <60 mL/min/1.73 m², and 2.9% had UACR ≥3.5 mg/mmol. Relative to being in the never-overweight latent class, being in the pubertal-onset– or always-overweight latent classes was associated with eGFRcys-defined CKD (OR, 2.04; 95% CI, 1.09-3.82). Associations with CKD defined by eGFRcr (OR, 1.27; 95% CI, 0.71-2.29) and UACR (OR, 1.33; 95% CI, 0.70-2.54) were less marked, but in the same direction. Adjustment for lifestyle and health factors had little impact on effect estimates.

Limitations: A low prevalence of CKD resulted in low statistical power. No documentation of chronicity for outcomes. All-white study population restricts generalizability.

Conclusions: Being overweight in early life was found to be associated with eGFRcys-defined CKD in later life. The associations with CKD defined by eGFRcr and UACR were less marked, but in the same direction. Reducing or preventing overweight in the early years of life may significantly reduce the burden of CKD in the population.

INDEX WORDS: Childhood obesity; chronic kidney disease; estimated glomerular filtration rate.

During recent decades, the prevalence of overweight and obesity has increased dramatically in many parts of the world,1 with further increases predicted in the coming years.2 Of particular concern is the growing global childhood obesity epidemic.3

Globally increasing cardiovascular mortality4 together with the recognition of kidney disease as a cardiovascular risk factor5 has led to greater interest in the relationship between obesity and kidney disease. A growing number of studies have concluded that adulthood obesity increases the risk of kidney disease6 and numerous studies have tracked obesity from childhood into adulthood.7 However, not many studies have directly examined the effect of childhood obesity on the risk of kidney disease, and consequently, our understanding is limited. A review of 6...
such studies determined that childhood obesity is associated with an elevated risk of kidney disease, as well as its progression and mortality, but all these studies were conducted in patients already with kidney disease rather than the general population. A more recent study of 1.2 million Israelis found overweight and obesity at age 17 years to be associated with a significantly increased risk of all-cause end-stage renal disease in a 25-year period.

We previously have found overweight in adulthood, particularly overweight starting in early adulthood, to be associated with reduced kidney function later in life in the Medical Research Council (MRC) National Survey of Health and Development (NSHD). In the present study, we extend our previous work to explore whether the increase in risk associated with overweight stretches back even farther, into early life. We used repeated measurements of body mass index (BMI) between ages 2 and 20 years to model early-life overweight trajectories, which we then related to measures of chronic kidney disease (CKD) at age 60-64 years.

METHODS

Participants

The NSHD is a socially stratified sample of 5,362 singletons 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 (when members of the cohort were aged 60-64 years), 2,856 eligible study participants (those known to be alive and with a known address in England, Scotland, or Wales) were invited for an assessment at 1 of 6 clinical research facilities. If they 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, 2,229 (78.0%) were assessed: 1,690 (59.2%) attended a clinic and 539 (18.9%) had a home visit.12

Measures

Height and weight were measured at ages 2, 4, 6, 7, 11, and 15 according to standard protocols and self-reported at age 20 years. BMI, defined as weight in kilograms divided by height in meters squared, was calculated at each age. We then used the international overweight cutoffs of Cole et al13 to determine the corresponding overweight status at each age. For clarity, those identified as overweight by this approach include both those traditionally labeled overweight and those labeled obese. Furthermore, in this report, we use the term overweight as a noun, as is customary with obese.

At the clinic or home visit at age 60-64 years, blood and urine samples were obtained and processed according to standardized protocols. Serum creatinine was measured by means of a kinetic version of the Jaffé method on a Siemens Dimension analyzer, and urinary albumin was measured by an immunoturbidimetric method on a Siemens BNI/ProSpec analyzer at the MRC Human Nutrition Research laboratory in Cambridge. Creatinine- and cystatin C–based estimated glomerular filtration rate (eGFRcr and eGFRcys, respectively) were calculated using the CKD Epidemiology Collaboration (CKD-EPI) formulas dating from 2009 and 2012, respectively.14,15 Urine albumin-creatinine ratio (UACR) was calculated with adjustment for storage time.

Based on KDIGO (Kidney Disease: Improving Global Outcomes) criteria,16 we defined CKD as either: (1) eGFRcr <60 mL/min/1.73 m², (2) eGFRcys <60 mL/min/1.73 m², or (3) UACR ≥3.5 mg/mmol. We analyzed each of these CKD outcomes separately, as well as a composite measure that indicated whether CKD was present on any one or more of the CKD outcomes. As a secondary outcome, we also analyzed cystatin C.

Several lifestyle and health factors were considered as potential confounders or mediators of the association between overweight trajectory during ages 2-20 years and later CKD: childhood socioeconomic position (SEP; manual labor/blue collar work vs nonmanual labor/white collar work) was derived from the father’s occupation when the study participant was aged 4 years; adulthood SEP (as described) was defined as the highest occupational class derived from the study participant’s and spouse’s occupations at age 53 years; previously derived smoking trajectory between ages 20 and 53 years; previously derived physical activity latent classes between ages 31 and 53 years; diabetes (self-reported physician-diagnosed diabetes by age 60-64 years, on diabetes medication at age 60-64 years, and hemoglobin A₁c level at age 60-64 years); and hypertension (previously derived systolic blood pressure latent trajectory between ages 36 and 53 years, on blood pressure medication at age 60-64 years, and measured systolic blood pressure at age 60-64 years).

Overweight at ages 36 and 53 years was considered as potential mediators. Height and weight, measured at ages 36 and 53 years using standard protocols, were used to calculate BMI, with overweight defined as BMI ≥25 kg/m².

Statistical Analyses

We first conducted longitudinal latent class analysis on the overweight indicator variables between ages 2 and 20 years. The objective of longitudinal latent class analysis is to decide how many latent classes are required to describe the data and categorize individuals into their most likely classes given their observed measurements. Analyses were restricted to study members with at least one BMI measurement between ages 2 and 20 years. Data missingness was handled using full information maximum likelihood under the assumption of missing at random.

Patterns of early-life (ages 2-20 years) overweight were found to differ between males and females, so separate longitudinal latent class analyses were conducted. We used a variety of different tools to decide how many classes were required because no single approach is commonly accepted.21 Posterior probabilities were derived to quantify the probability with which an individual with a given early-life overweight pattern belonged to each latent class. We investigated to what extent the latent classes were associated with birth weight.

Main Analyses

To account for the potential bias caused by missing data, we conducted our analyses using a multiple imputation approach.22,23 In addition to all variables included in the analysis models, the imputation model also included occupation at other ages in adulthood, further repeated measures of adulthood BMI, repeated
measures of adulthood waist to hip ratio, birth weight, achieved educational levels of the study member and their parents, and response at the age 60- to 64-year data collection (eg, clinic/home visit, temporary/permanent refusal, and untraced). Interactions with sex were included in the imputation model for all variables. Study members who were known to have died prior to or during the age 60- to 64-year data collection were excluded from the multiple imputation analysis. Fifty imputed data sets were obtained through chained equations.24,25

Each of the 4 binary CKD outcomes was related to the resultant overweight latent classes using logistic regression, weighted by the longitudinal latent class analysis posterior class membership probabilities and minimally adjusted for sex and age at CKD measurements.

With the exception of childhood SEP, identifying lifestyle variables (SEP, smoking, and physical activity) as either potential confounders or mediators of the association between early-life overweight and later CKD is not straightforward. However, adult-adult diabetes and hypertension more clearly are potential mediators of the association of interest. The extent to which these lifestyle and health factors confounded or mediated the association between early-life overweight and later CKD was examined by adding, in turn, childhood and adulthood SEP, lifetime smoking trajectory, midadulthood physical activity levels, diabetes (all 3 variables), hypertension (all 3 variables), and finally, all lifestyle and health factors to the minimally adjusted models.

The observed overall prevalence of CKD varied between the different measures, from 1.7% (eGFR_cys) to 2.9% (UACR). Median cystatin C level was 0.81

The longitudinal latent class analysis was conducted using Mplus 6 (Muthén & Muthén), with the remaining analysis, including the multiple imputation, performed using Stata 12 (StataCorp).

RESULTS

Study Participants and Longitudinal Latent Class Analysis

A flow diagram showing inclusion in the early-life (ages 2-20 years) overweight longitudinal latent class analysis and multiple imputation analysis is shown in Fig S1 (provided as online supplementary material). Of the original 5,362 study members in the cohort, 4,884 had at least one BMI measurement between ages 2 and 20 years and were included in the longitudinal latent class analysis. Of these, 77.6% had at least 5 of the 7 BMI measurements. The prevalence of early-life overweight decreased from 35.1% at age 2 years to 7.1% at age 7 years before increasing to 12.6% at age 20 years (Table S1).

In the longitudinal latent class analysis, all metrics suggested that 4 early-life overweight latent classes were required for both males and females (results not shown). These patterns of early-life overweight can be considered as never (71.4% of males and 80.6% of females), prepubertal only (21.0% and 8.9%), pubertal-onset (5.0% and 6.6%), and always (2.7% and 3.9%; Figs 1 and 2). Males and females in the never-overweight latent class had the lowest average birth weight (3.44 and 3.30 kg, respectively), and those in the always-overweight class had the highest (3.68 and 3.49 kg), with birth weights in the prepubertal-only (3.60 and 3.47 kg) and pubertal-onset (3.61 and 3.39 kg) overweight classes falling in between.

The observed overall prevalence of CKD varied between the different measures, from 1.7% (eGFR_cys) to 2.9% (UACR). Median cystatin C level was 0.81
Overall distributions of all variables included in the analysis are listed in Table 1. The prevalence of CKD differed between the early-life BMI latent classes (Table 1). For both eGFR<sub>cr</sub> and eGFR<sub>cys</sub>, the lowest prevalence was in the never-overweight latent class (2.0% and 1.4%, respectively), with the highest prevalence in the pubertal-onset overweight latent class (4.6% and 5.3%). For UACR, the highest prevalence similarly was in the

| Table 1. Distributions of Variables Stratified by Early-Life Overweight Latent Class, Weighted by Posterior Probability of Class Membership |
|-----------------------------------------------|
|                                   | No. With Available Data | Total (N = 4,884*) | Never (n = 4,037) | Prepubertal Only (n = 491) | Pubertal Onset (n = 209) | Always (n = 147) |
|-----------------------------------------------|
| Age at examination (y)                      |                          |                     |                   |
| 2,197                                        | 63.6 [1.3]               | 63.6 [1.3]         | 63.7 [1.5]       | 63.7 [1.6]             | 63.6 [1.3]             |
| eGFR<sub>cr</sub> at age 60-64 y (mL/min/1.73 m<sup>2</sup>) | 1,826                     | 96.0 [16.3]        | 96.3 [16.1]     | 95.5 [16.4]           | 94.6 [16.2]           | 96.8 [16.5]    |
| UACR at age 60-64 y (mg/mmol)               | 2,022                     | 96.9 [19.0]        | 96.9 [18.8]     | 98.3 [18.9]           | 92.1 [20.5]           | 96.4 [19.1]    |
| Cystatin C at age 60-64 y (mg/L)            | 2,023                     | 0.81 [0.16]        | 0.81 [0.16]     | 0.81 [0.16]           | 0.84 [0.18]           | 0.82 [0.14]    |
| HbA<sub>1c</sub> at age 60-64 y (%)         | 2,014                     | 5.7 [0.5]          | 5.7 [0.5]       | 5.7 [0.4]             | 5.7 [0.6]             | 5.7 [0.5]      |
| SBP at age 60-64 y (mm Hg)                  | 2,177                     | 133 [22]           | 132 [22]        | 133 [22]             | 135 [23]             | 134 [21]       |
| eGFR<sub>cr</sub> < 60 mL/min/1.73 m<sup>2</sup> at age 60-64 y | 1,826                     | 2.3                | 2.0             | 2.3                  | 4.6                  | 2.9            |
| eGFR<sub>cys</sub> < 60 mL/min/1.73 m<sup>2</sup> at age 60-64 y | 2,022                     | 1.7                | 1.4             | 1.7                  | 5.3                  | 3.2            |
| UACR < 0.5 mg/mmol at age 60-64 y           | 2,141                     | 0.54 [0.43]        | 0.54 [0.40]     | 0.61 [0.50]           | 0.62 [0.53]           |                |
| CKD by composite measure at age 60-64 y     | 1,799                     | 5.5                | 5.1             | 5.0                  | 11.9                 | 5.8            |
| Manual labor/blue collar work               |                          |                     |                   |
| Study member’s parents                      | 4,473                     | 59.2               | 58.9            | 59.8                 | 63.9                 | 56.4           |
| Study member at age 53 y                    | 2,828                     | 21.0               | 20.4            | 23.6                 | 25.6                 | 15.3           |
| Lifetime smoking trajectory                 | 3,352                     |                     |                   |
| Never smoker                                | 28.0                      | 28.6               | 25.8            | 27.5                 | 26.5                 |                |
| Predominantly nonsmoker                     | 32.6                      | 32.7               | 32.4            | 30.2                 | 36.5                 |                |
| Predominantly smoker                        | 21.0                      | 20.9               | 21.6            | 19.9                 | 24.7                 |                |
| Lifelong smoker                             | 18.3                      | 17.8               | 20.3            | 22.5                 | 12.3                 |                |
| Time sitting down during day at age 36 y    | 3,238                     |                     |                   |
| Much                                        | 26.4                      | 26.0               | 27.5            | 27.8                 | 27.5                 |                |
| Average                                     | 34.3                      | 34.5               | 34.9            | 30.1                 | 35.3                 |                |
| Little                                      | 39.3                      | 39.5               | 37.7            | 42.2                 | 37.2                 |                |
| Low walking latent class at age 36-43 y     | 3,522                     | 41.8               | 41.1            | 44.6                 | 43.9                 | 42.9           |
| Low cycling latent class at age 31-43 y     | 3,711                     | 87.4               | 87.4            | 86.9                 | 87.7                 | 89.8           |
| Leisure time physical activity latent class at age 36-53 y | 3,601                     |                     |                   |
| Low                                         | 46.8                      | 46.4               | 46.7            | 53.3                 | 44.9                 |                |
| Gardening and DIY                          | 18.2                      | 17.5               | 20.2            | 19.9                 | 20.8                 |                |
| Sport and leisure                          | 35.0                      | 36.1               | 33.1            | 26.9                 | 34.3                 |                |
| Self-reported diabetes by age 60-64 y       | 2,417                     | 7.5                | 6.8             | 7.4                  | 12.8                 | 14.0           |
| Receiving diabetes treatment at age 60-64 y | 2,585                     | 5.5                | 5.0             | 5.6                  | 7.6                  | 13.1           |
| Increased/high midlife SBP trajectory       | 3,589                     | 6.5                | 6.7             | 4.9                  | 6.6                  | 8.9            |
| Receiving antihypertensive treatment at age 60-64 y | 2,585                     | 29.7               | 29.2            | 28.4                 | 35.1                 | 36.3           |
| Overweight at age 36 y                      | 3,333                     | 35.0               | 28.9            | 44.0                 | 68.4                 | 75.4           |
| Overweight at age 53 y                      | 2,895                     | 66.8               | 63.2            | 73.2                 | 85.8                 | 87.7           |

Note: With the exception of study members being given as number, values in upper section of table are given as median [interquartile range] and values in lower section are given as percentage.

Abbreviations: CKD, chronic kidney disease; DIY, do-it-yourself activities; eGFR<sub>cr</sub>, creatinine-based estimated glomerular filtration rate; eGFR<sub>cys</sub>, cystatin C-based estimated glomerular filtration rate; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; SBP, systolic blood pressure; UACR, urinary albumin-creatinine ratio.

*Of original 5,362 study members in cohort, 4,884 had one or more body mass index measurement between ages 2 and 20 years and were included in longitudinal latent class analysis.

The examination in question occurred between October 2006 and February 2011, when cohort members were aged 60-64 years.
pubertal-onset overweight latent class (4.5%), although the lowest prevalence was in the always-overweight latent class (1.8%). Distributions of all variables included in the analysis within each early-life BMI latent class also are listed in Table 1.

There were very few study participants in the always-overweight latent class with CKD, so for the purpose of the remaining analyses, the pubertal-onset and always-overweight latent classes were combined. However, although there was insufficient power to formally test it, there was a suggestion that CKD risk was greater in the pubertal-onset overweight latent class than in the always-overweight latent class.

Main Analyses

As shown in Fig S1, 4,340 study members were eligible for both the longitudinal latent class analysis and multiple imputation procedures and were included in the analysis. There was evidence that, relative to being in the never-overweight latent class, being in the pubertal-onset or always-overweight latent classes was associated with CKD defined using eGFRcr (odds ratio [OR], 1.27; 95% CI, 0.71-2.29) and UACR (OR, 1.33; 95% CI, 0.70-2.54) were less marked, but in the same direction. There also was evidence of an association with the composite CKD measure (OR, 1.51; 95% CI, 1.03-2.20). For none of the outcomes was there evidence that being in the prepubertal-only overweight latent class increased the risk of reduced kidney function relative to the never-overweight latent class.

Adjustment for lifestyle and health factors had little impact on effect estimates (Tables 2 and 3). Adjustment for diabetes and hypertension generally resulted in the greatest attenuation. In the fully adjusted models (Table 3, model 7), there remained some evidence of an association with CKD defined using eGFRcr (OR, 1.88; 95% CI, 0.99-3.58) or the composite measure (OR, 1.39; 95% CI, 0.94-2.04).

All effect estimates showed greater attenuation when adjusted for overweight at age 36 years than when adjusted for overweight at age 53 years (Table 4). For example, the composite CKD measure OR for pubertal onset or always overweight was attenuated from 1.51 to 1.18 on adjustment for overweight at age 36 years, but to only 1.39 on adjustment for overweight at age 53 years.

### Table 2. ORs for CKD at Age 60-64 Years by Early-Life Overweight Latent Class, Models 1-3

| CKD Definition and Early-Life Overweight Latent Class | Percentage in Latent Class | Model 1* | Model 2b | Model 3c |
|-------------------------------------------------------|-----------------------------|----------|----------|----------|
| CKD by eGFRcr                                         |                             |          |          |          |
| Never                                                 | 76.0                        | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prepubertal only                                       | 15.1                        | 1.00 (0.66-1.53) | 1.00 (0.66-1.52) | 1.00 (0.66-1.53) |
| Pubertal onset/always                                  | 8.9                         | 1.27 (0.71-2.29) | 1.26 (0.70-2.27) | 1.27 (0.70-2.29) |
| CKD by eGFRcys                                         |                             |          |          |          |
| Never                                                 | 76.0                        | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prepubertal only                                       | 15.1                        | 1.21 (0.70-2.11) | 1.20 (0.69-2.07) | 1.19 (0.68-2.08) |
| Pubertal onset/always                                  | 8.9                         | 2.04 (1.09-3.82) | 1.98 (1.06-3.70) | 2.00 (1.06-3.79) |
| CKD by UACR                                           |                             |          |          |          |
| Never                                                 | 76.0                        | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prepubertal only                                       | 15.1                        | 0.93 (0.60-1.42) | 0.93 (0.60-1.42) | 0.92 (0.60-1.41) |
| Pubertal onset/always                                  | 8.9                         | 1.33 (0.70-2.54) | 1.32 (0.69-2.53) | 1.32 (0.69-2.52) |
| Composite CKD measure                                  |                             |          |          |          |
| Never                                                 | 76.0                        | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prepubertal only                                       | 15.1                        | 0.99 (0.74-1.34) | 0.99 (0.74-1.33) | 0.99 (0.74-1.33) |
| Pubertal onset/always                                  | 8.9                         | 1.51 (1.03-2.20) | 1.49 (1.02-2.17) | 1.50 (1.02-2.19) |

*Note: Multiple imputation analysis (n = 4,340). Abbreviations and definitions: CI, confidence interval; CKD, chronic kidney disease (eGFR<sub>cr</sub> or eGFR<sub>cys</sub> < 60 mL/min/1.73 m<sup>2</sup> or UACR ≥ 3.5 mg/mmol); eGFR<sub>cr</sub>, creatinine-based estimated glomerular filtration rate; eGFR<sub>cys</sub>, cystatin C–based estimated glomerular filtration rate; OR, odds ratio; UACR, urinary albumin-creatinine ratio.

*Model 1: adjusted for sex and age at CKD measurements.

*Model 2: adjusted for sex, age at CKD measurements, and childhood and adulthood socioeconomic position.

*Model 3: adjusted for sex, age at CKD measurements, and lifetime smoking trajectory.

*Average across all 50 imputed data sets.
Supplementary Analyses

Being in the pubertal-onset or always-overweight latent classes also was associated with a 0.027 (95% CI, 0.007-0.048) mg/L increase in cystatin C level relative to being in the never-overweight latent class (Table S2). Adjustment for lifestyle and health factors again had little impact on this effect estimate (Table S2 and b), and it showed greater attenuation when adjusted for overweight at age 36 years than when adjusted for overweight at age 53 years (Table S2c).

Complete case analyses of the binary CKD outcomes included between 1,799 (composite CKD measure) and 2,141 (UACR) study members. Estimated associations between early-life overweight latent class and later CKD were stronger than those in the multiple imputation analysis for eGFR_\text{cr} and eGFR_\text{cys}, but similar for UACR (Table S2a). However, the CIs were much wider due to the reduced sample size. There remained strong evidence of associations for eGFR_\text{cys} and the composite CKD measure, with associations for eGFR_\text{cr} and UACR less marked but in the same direction. Additional adjustment for lifestyle factors again resulted in little attenuation of the effect estimates (Table S2b and c). As in the multiple imputation analysis, all effect estimates showed greater attenuation when adjusted for overweight at age 36 years than when adjusted for overweight at age 53 years (Table S3).

Complete case results for cystatin C were in line similarly with the multiple imputation results (Table S4).

DISCUSSION

In a large population-based prospective study, we found that overweight throughout early life or becoming overweight in the period from puberty to age 20 years was associated with CKD at age 60-64 years assessed using eGFR_\text{cys}. This association was supported by less marked associations with eGFR_\text{cr} and UACR. Confounding or mediation by childhood and adulthood SEP, lifetime smoking trajectory, and midadulthood physical activity levels did not explain the observed associations, and mediation by diabetes and hypertension was limited.

The associations were attenuated to a far greater extent when adjusted for overweight at age 36 years than when adjusted for overweight at age 53 years. This suggests that: (1) being overweight in early adulthood is particularly harmful for later CKD (corresponding to our previous findings in this cohort), and/or (2) early-life and late-adulthood overweight

| CKD Definition and Early-Life Overweight Latent Class | Model 4* | Model 5b | Model 6c | Model 7d |
|-------------------------------------------------------|----------|----------|----------|----------|
| **CKD by eGFR_\text{cr}**                           |          |          |          |          |
| Never                                                 | 1.00     | 1.00     | 1.00     | 1.00     |
| Prepubertal only                                      | 1.00 (0.66-1.53) | 1.01 (0.67-1.54) | 1.02 (0.67-1.55) | 1.02 (0.67-1.56) |
| Pubertal onset/always                                 | 1.27 (0.70-2.29) | 1.23 (0.68-2.23) | 1.23 (0.68-2.23) | 1.20 (0.66-2.19) |
| **CKD by eGFR_\text{cys}**                           |          |          |          |          |
| Never                                                 | 1.00     | 1.00     | 1.00     | 1.00     |
| Prepubertal only                                      | 1.22 (0.70-2.12) | 1.23 (0.70-2.14) | 1.23 (0.71-2.13) | 1.20 (0.69-2.12) |
| Pubertal onset/always                                 | 2.04 (1.08-3.85) | 1.97 (1.05-3.69) | 1.96 (1.04-3.67) | 1.88 (0.99-3.58) |
| **CKD by UACR**                                       |          |          |          |          |
| Never                                                 | 1.00     | 1.00     | 1.00     | 1.00     |
| Prepubertal only                                      | 0.93 (0.60-1.42) | 0.93 (0.61-1.43) | 0.94 (0.61-1.45) | 0.94 (0.61-1.45) |
| Pubertal onset/always                                 | 1.29 (0.67-2.47) | 1.26 (0.66-2.41) | 1.24 (0.65-2.39) | 1.18 (0.61-2.27) |
| **Composite CKD measure**                            |          |          |          |          |
| Never                                                 | 1.00     | 1.00     | 1.00     | 1.00     |
| Prepubertal only                                      | 1.00 (0.74-1.34) | 1.00 (0.75-1.35) | 1.01 (0.75-1.36) | 1.01 (0.75-1.36) |
| Pubertal onset/always                                 | 1.48 (1.02-2.17) | 1.45 (0.99-2.13) | 1.44 (0.98-2.11) | 1.39 (0.94-2.04) |

Note: Multiple imputation analysis (n = 4,340).

Abbreviations and definitions: CI, confidence interval; CKD, chronic kidney disease (defined as eGFR_\text{cr} or eGFR_\text{cys} < 60 mL/min/1.73 m² or urine ACR ≥ 3.5 mg/mmol); eGFR_\text{cr}, creatinine-based estimated glomerular filtration rate; eGFR_\text{cys}, cystatin C–based estimated glomerular filtration rate; OR, odds ratio; UACR, urinary albumin-creatinine ratio.

*Model 4: adjusted for sex, age at CKD measurements, and midadulthood physical activity trajectories.

bModel 5: adjusted for sex, age at CKD measurements, and diabetes.

cModel 6: adjusted for sex, age at CKD measurements, and hypertension.

dModel 7: adjusted for sex, age at CKD measurements; childhood and adulthood socioeconomic position, lifetime smoking trajectory, midadulthood physical activity trajectories, diabetes, and hypertension.
have independent effects on CKD risk. However, this finding also may be due in part to the stronger associa-
tion of early-life overweight with overweight at age
36 years than overweight at age 53 years.

To our knowledge, there are no existing studies of
the effect of overweight throughout early life on later
kidney disease in general population cohorts. In a
review of studies examining the association between
obesity and kidney disease, Wang et al identified 6
cohort studies in youth, all of which involved partici-
pants who were either kidney disease patients or
transplant recipients. In addition, the variety of out-
comes and relatively short follow-up periods make
direct comparison with the present study difficult.
Wang et al concluded that high BMI or obesity in
early life is associated with an increased risk of
kidney disease. This finding is certainly not at odds
with ours.

In a recent large population-based cohort study,
Vivante et al found overweight and obesity at age 17
years to be associated with significantly increased risk
of all-cause end-stage renal disease in a 25-year
period. Although their adjusted hazard ratios of 3.00
(95% CI, 2.50-3.60) for overweight and 6.89 (95%
CI, 5.52-8.59) for obesity appear somewhat stronger
than the ORs reported in the present study, differences
in definition of both the exposure and outcome make
comparison difficult.

Associations between early-life overweight and
many adverse health outcomes in later life are now
acknowledged, and several previous studies have
looked in more detail at specific patterns of early-life
weight gain. In the same cohort as the present study,
Hardy et al highlighted excessive pubertal BMI gain
as being associated particularly strongly with later
blood pressure. Our observation that the pubertal-
onset overweight latent class seemed at somewhat
higher risk of later CKD than the always-overweight
latent class hints at a similar pattern for CKD.

Previous studies also have found children who
were overweight before puberty but returned to nor-
mal weight during puberty to have similar levels of
later blood pressure and other cardiovascular risk
factors as those who remained normal weight
throughout. Our finding that CKD risk did not differ
between the prepubertal-only and never-overweight
latent classes is in agreement with these previous
results.

Studies also have suggested that individuals who
were born small but then rapidly gained weight during
early life are at particularly high risk of later hyperten-
sion or diabetes. However, the pubertal-onset

### Table 4. ORs for CKD at Age 60-64 Years by Early-Life Overweight Latent Class, Adjusted for Later-Life Overweight

| CKD Definition and Early-Life Overweight Latent Class | Model 1a | Model 1 + Overweight at Age 36 yb | Model 1 + Overweight at Age 53 yc |
|-------------------------------------------------------|----------|----------------------------------|----------------------------------|
| CKD by eGFR<sub>cr</sub>                              |          |                                  |                                  |
| Never                                                 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prepubertal only                                      | 1.00 (0.66-1.53) | 0.94 (0.61-1.43) | 0.98 (0.64-1.48) |
| Pubertal onset/always                                 | 1.27 (0.71-2.29) | 1.01 (0.54-1.86) | 1.16 (0.64-2.12) |
| CKD by eGFR<sub>cys</sub>                             |          |                                  |                                  |
| Never                                                 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prepubertal only                                      | 1.21 (0.70-2.11) | 1.11 (0.64-1.92) | 1.16 (0.67-2.02) |
| Pubertal onset/always                                 | 2.04 (1.09-3.82) | 1.54 (0.82-2.86) | 1.80 (0.95-3.38) |
| CKD by UACR                                           |          |                                  |                                  |
| Never                                                 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prepubertal only                                      | 0.93 (0.60-1.42) | 0.87 (0.57-1.34) | 0.91 (0.59-1.40) |
| Pubertal onset/always                                 | 1.33 (0.70-2.54) | 1.09 (0.57-2.06) | 1.25 (0.66-2.39) |
| Composite CKD measure                                 |          |                                  |                                  |
| Never                                                 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prepubertal only                                      | 0.99 (0.74-1.34) | 0.93 (0.69-1.24) | 0.97 (0.72-1.30) |
| Pubertal onset/always                                 | 1.51 (1.03-2.20) | 1.18 (0.80-1.75) | 1.39 (0.95-2.04) |

Note: Multiple imputation analysis (n = 4,340).
Abbreviations and definitions: CI, confidence interval; CKD, chronic kidney disease (defined as eGFR<sub>cr</sub> or eGFR<sub>cys</sub> 60 mL/min/1.73 m<sup>2</sup> or urine ACR 3.5 mg/mmol); eGFR<sub>cr</sub> creatinine-based estimated glomerular filtration rate; eGFR<sub>cys</sub> cystatin C-based estimated glomerular filtration rate; OR, odds ratio; UACR, urinary albumin-creatinine ratio.

*aModel 1: adjusted for sex and age at CKD measurements (data repeated from Table 2).
*bModel 2: adjusted for sex, age at CKD measurements, and overweight at age 36 years.
*cModel 3: adjusted for sex, age at CKD measurements, and overweight at age 53 years.
overweight latent class identified in the present analysis was found to have a relatively high mean birth weight in both males and females, so our results cannot be explained by this pathway.

The mechanisms relating early-life BMI to later CKD are not well researched. Overweight children are at higher risk of developing high blood pressure and diabetes, although evidence for effects independent of adulthood overweight is lacking. Overweight may have independent associations with blood pressure that may precede decreased kidney function. Animal studies suggest that obesity is followed by initial glomerular hyperfiltration, the development of albuminuria, and subsequent decline in eGFR. This may explain why we did not observe strong associations of early-life overweight with UACR; one could speculate that at age 60-64 years, those who were overweight from early in life may well have passed through the early albuminuria stage, although the data do not allow the sequence of events to be disentangled.

There are many strengths to this analysis. BMI measurements were available at regular intervals throughout early life and calculating overweight status using age-specific cutoffs allowed the variability in actual ages at measurement to be taken into account. Furthermore, the availability of several different measures of CKD allowed a more thorough analysis.

The use of full information maximum likelihood in the longitudinal latent class analysis allowed the inclusion of all study members with at least one early-life BMI measurement under the assumption of missing at random. The longitudinal latent class analysis models fit the data well and the resultant latent classes were clearly separated and easily interpreted.

Cohort members remaining in the NSHD at the time of data collection at age 53 years and at age 60-64 years have been determined as generally representative of native-born adults living in England, Scotland, and Wales. We thus are confident that our analysis sample retained the representativeness of the study population as a whole. Use of multiple imputation allowed us to account for the potential bias caused by missing data.

There were limitations to the study. Calculation of eGFR, rather than measuring GFR directly, may have resulted in some misclassification of CKD. The lack of repeated measurements of kidney function meant that we were unable to ascertain CKD using the recommended definition of reduced kidney function for at least 3 months. This is likely to introduce nondifferential misclassification, meaning that the true association is even stronger than described here. In addition, the low prevalence of CKD in this cohort resulted in low statistical power. Although the similarity in findings across the different measures of CKD and cystatin C suggests robustness to our findings, it is important that they are replicated in larger general population cohorts. Finally, although we had good coverage of different UK regions and social class groupings, because the NSHD study population is all white, our findings cannot necessarily be extrapolated to the nonwhite British population.

It should be noted that members of this cohort experienced childhood in the 1950s, when overweight/obesity was far less prevalent. Only 7% of study members were in the pubertal-onset or always-overweight latent classes, whereas ~40% of modern children in the Americas and Europe are thought to be overweight or obese. Thus, the absolute impact of any effect of early-life overweight on CKD is likely to be substantial at the population level.

In conclusion, being overweight throughout early life or becoming overweight in the period from puberty to age 20 years was found to be associated with CKD in later life. Reducing or preventing overweight in early life may significantly reduce the burden of CKD in the population.

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SUPPLEMENTARY MATERIAL

Table S1: Prevalence of overweight at each age in early life in the MRC NSHD.
Table S2: Linear regression coefficients for cystatin C level at age 60-64 by early-life overweight latent class.
Table S3: ORs for CKD at age 60-64 by early-life overweight latent class, by complete case analyses.
Table S4: Linear regression coefficients for cystatin C level at age 60-64 by early-life overweight latent class, by complete case analyses.
Figure S1: Flow diagram showing inclusion in early-life overweight latent class analysis and multiple imputation analysis.

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