SUPPLEMENTAL MATERIAL

COMPLETE METHODS

Participants

The MRC NSHD is a socially stratified sample of 5362 singleton children born in one week in March 1946 in England, Scotland and Wales. Medical and social data have been collected 23 times by home visits, medical examinations and postal questionnaires.[1]

Of the original sample, the study team was still in contact with 3163 (59%) prior to the most recent data collection at age 60-64 years. Of the original cohort 718 (13.4%) had died, 594 (11.1%) had previously withdrawn from the study, 567 (10.6%) lived abroad and 320 (5.9%) had been untraceable for more than ten years.

Study members were invited for clinic visits between October 2007 and February 2011. If study members were unable or unwilling to come to one of the six Clinical Research Facilities across the country they were offered a slightly less comprehensive examination carried out in their own home by a trained nurse. Of the 3163 study members in the target sample, 2229 (70.5%) had a visit, of whom 1690 (53.4%) attended a clinic and 539 (17.0%) had a home visit.[2]

Measures

Adult heights and weights were measured at ages 36, 43, 53 and 60-4 years, and self-reported at ages 20 and 26. BMI, defined as weight (kg)/height $(m)^2$, was calculated at each age. A binary variable indicating overweight was calculated at each age, using the standard cut point of 25 kg/m^2.

The main exposure of interest was the age at which a study participant first became overweight (26, 36, 43, 53, 60-4 or never). This was derived assuming that once an individual became overweight they remained overweight, but a sensitivity analysis was also conducted in which any individuals who did not remain overweight once they had first become overweight (11.9% of those initially included) were excluded. Overweight at each separate age (20, 26, 36, 43, 53 and 60-4) was considered as a secondary analysis.

At the clinic or home visit at age 60-4, blood and urine samples were taken and processed according to standardised protocols. Serum creatinine was measured by means of a kinetic version of the Jaffe method using a Siemens Dimension Xpand analyser at the MRC Human Nutrition Research (HNR) 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 analyser and urinary albumin was measured by an immunoturbidimetric method on a Siemens BNII/ProSpec analyser at the MRC Human Nutrition Research (HNR) laboratory in Cambridge.

Creatinine-based estimated glomerular filtration rate (eGFR) and cystatin C-based eGFR were calculated using the CKD-EPI formulae[3,4]. Urine albumin-creatinine ratio (UACR) was calculated with adjustment for storage time.

Four different indicators of reduced renal function at age 60-4 were used: i) creatinine-based eGFR < 60 ml/min/1.73m^2; ii) cystatin C-based eGFR < 60 ml/min/1.73m^2; iii) UACR ≥ 3.5 mg/mmol; iv) a composite CKD measure indicating whether any one or more of the previous three indicators were present.

Childhood socioeconomic position (SEP) (manual/non-manual; derived from father's reported occupation when study member was age 4) and adulthood SEP (manual/non-manual; highest occupational class derived from study member's and their spouse's reported occupations at age 53) were considered as potential confounders.

Diabetes (self-reported doctor diagnosed diabetes by age 60-4, on diabetes medication at age 60-4, HbA1c level at age 60-4) and hypertension (previously derived systolic blood pressure (SBP) latent trajectory between ages 36 and 53,[5] on blood pressure medication at age 60-4, measured SBP at age 60-4) were considered as mediating factors.

Some previous studies have indicated that central obesity is a stronger predictor of CKD than BMI.[6] A final analysis thus examined whether adulthood waist-hip ratio was associated with kidney function at age 60-4 in the same way as adulthood overweight. Waist-hip ratios at ages 43, 53 and 60-4 were derived using repeated measures of waist and hip circumferences.

Statistical analyses

Main analyses

Each kidney function outcome was related to age at first overweight using logistic regression. Models were minimally adjusted for sex and age (Model 1), then additionally adjusted for childhood and adulthood SEP (Model 2). A similar approach has previously been used to assess the relationship between patterns of overweight during adulthood and blood pressure at age 53 in the NSHD.[7]

To investigate the potential bias caused by missing data we utilised a multiple imputation (MI) approach.[8,9] As well as all the variables included in the analysis models (BMI at each age in adulthood, serum creatinine and cystatin C, UACR, sex, age at examination, father's occupation when study member was age 4, study member's and their spouse's occupation at age 53, self-reported doctor diagnosed diabetes by age 60-4, on diabetes medication at age 60-4, measured HbA1c at age 60-4, mid-adulthood blood pressure latent trajectories, on hypertension medication at age 60-4, measured SBP at age 60-4, repeated measures of adulthood waist-hip ratio) the imputation model also included occupation at other ages in adulthood, mid-adulthood physical activity latent classes,[10] lifetime smoking trajectory,[11] repeated measures of childhood BMI, birth weight, achieved educational levels of the study member and their parents, and response at the age 60-4 data collection (e.g. clinic/home visit, temporary/permanent refusal, 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 60-4 data collection were excluded from the MI analysis. Fifty imputed data sets were obtained via chained equations.[12, 13]

Supplementary analyses

The analysis relating each kidney function outcome to age at first overweight outlined above was repeated using complete cases only as a comparison with the MI results. A sensitivity

analysis was conducted in which any individuals who did not remain overweight once they had first become overweight were excluded.

We investigated the associations between each kidney function outcome and overweight status at each age using logistic regression, using both a MI approach and a complete case analysis for comparison. Models were again minimally adjusted for sex and age (Model 1), then additionally adjusted for childhood and adulthood SEP (Model 2).

The extent to which the association between age at first overweight and kidney function at age 60-4 was mediated by diabetes and hypertension was examined by adding each of these to the models for age at first overweight and examining the extent to which the effect estimates were attenuated.

Associations between waist-hip ratio at each age and kidney function at age 60-4 were examined in the same way as overweight at each age. Waist-hip ratio at ages 43 and 53 were then added in turn to the models for age at first overweight to examine whether the association remained once waist-hip ratio was taken into account.

Finally, population attributable fractions (PAFs) for the composite CKD measure were calculated using the MI model adjusted for age, sex and childhood and adulthood SEP.[14] This represents the proportion of CKD cases occurring in the total population that would have been avoided if nobody had become overweight. PAFs were calculated using the study sample and for the current US population. For the latter, overweight prevalences at the appropriate ages (26, 36, 43, 53 and 60-4 years) were derived by interpolating the NHANES 2009-10 estimates of Flegal et al,[15] with the proportion of people becoming overweight in

each interval calculated as the difference between the two consecutive prevalences (for example, the proportion of people becoming overweight between ages 26 and 36 is the difference between the overweight prevalence at age 36 and the overweight prevalence at age 26).

In none of the models was there any evidence of interactions with sex, so combined male and female models are presented throughout.

The analysis was performed using Stata 12.[16]

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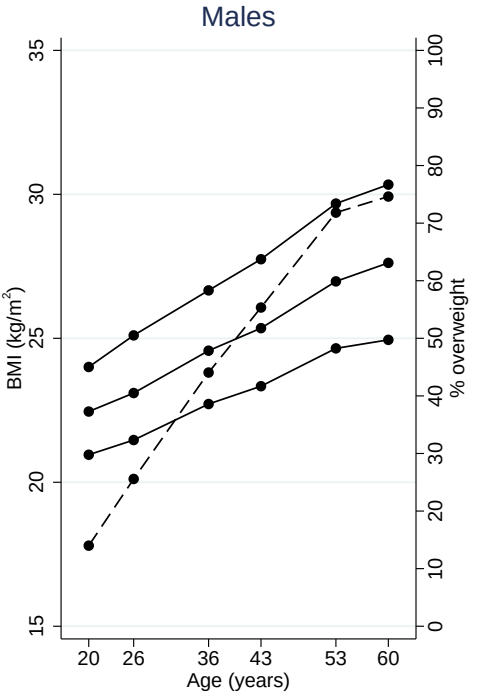
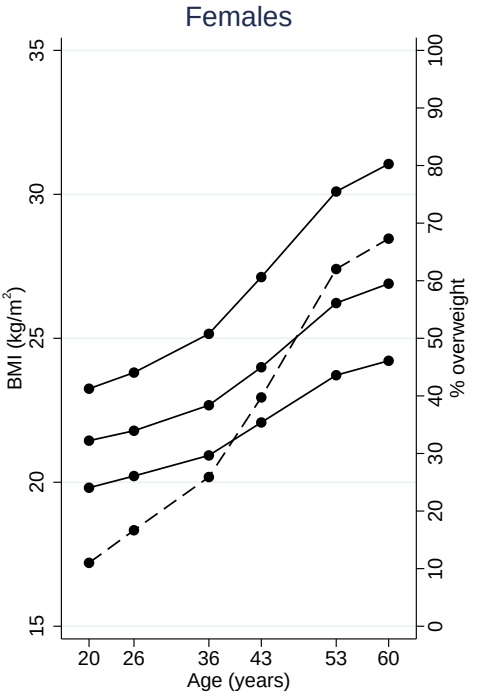
FIGURE LEGEND

Figure 1. Median and upper and lower quartiles of body mass index (BMI) (solid lines) and % of individuals overweight (BMI $\geq$ 25 kg/m^2) (dashed line) in males and females at each age in adulthood. Adapted from Wills et al.[7]


Males
BMI (kg/m^2)
% overweight
Age (years)
15
20
25
30
35
0
10
20
30
40
50
60
70
80
90
100
20
26
36
43
53
60


Females
BMI (kg/m^2)
% overweight
Age (years)
15
20
25
30
35
0
10
20
30
40
50
60
70
80
90
100
20
26
36
43
53
60

TABLES

Table 1. Odds ratios (ORs) for estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 by age first overweight. Restricted to study participants non-missing for childhood and adulthood SEP.

Age first overweight (years)	n (%) of total first overweight at this age	n (%) of those first overweight at this age with eGFR < 60 ml/min/1.73m^2	Model 1			Model 2		
			OR	95 % CI	*P* for trend	OR	95 % CI	*P* for trend
Creatinine-based eGFR (n = 1534)								
26	270 (17.6)	8 (3.0)	3.09	1.04, 9.12		2.72	0.90, 8.18	
36	221 (14.4)	6 (2.7)	2.90	0.91, 9.26		2.93	0.90, 9.49	
43	215 (14.0)	4 (1.9)	1.71	0.48, 6.15	0.03	1.78	0.49, 6.41	0.05
53	309 (20.1)	6 (1.9)	1.77	0.56, 5.55		1.85	0.59, 5.84	
60-4 or never	519 (33.8)	6 (1.2)	1.00			1.00		
Cystatin C-based eGFR (n = 1684)								
26	295 (17.5)	10 (3.4)	3.29	1.27, 8.54		2.57	0.97, 6.79	
36	246 (14.6)	9 (3.7)	3.64	1.37, 9.70		3.47	1.28, 9.39	
43	236 (14.0)	7 (3.0)	2.40	0.85, 6.73	0.001	2.42	0.86, 6.84	0.01
53	345 (20.5)	4 (1.2)	0.84	0.25, 2.83		0.87	0.26, 2.93	
60-4 or never	562 (33.4)	8 (1.4)	1.00			1.00		

Model 1: Adjusted for age at examination and sex. Model 2: Additionally adjusted for childhood and adulthood SEP.

Table 2. Odds ratios (ORs) for urine albumin-creatinine ratio (UACR) ≥ 3.5mg/mmol by age first overweight (n = 1772). Restricted to study participants non-missing for childhood and adulthood SEP.

Age first overweight (years)	n (%) of total first overweight at this age	n (%) of those first overweight at this age with UACR ≥ 3.5mg/mmol	Model 1			Model 2		
			OR	95 % CI	*P* for trend	OR	95 % CI	*P* for trend
26	312 (17.6)	15 (4.8)	2.51	1.10, 5.71		2.49	1.08, 5.74	
36	269 (15.2)	15 (5.6)	2.91	1.28, 6.64		2.84	1.24, 6.51	
43	241 (13.6)	5 (2.1)	1.14	0.38, 3.38	0.01	1.12	0.38, 3.33	0.01
53	361 (20.4)	8 (2.2)	1.28	0.50, 3.29		1.27	0.49, 3.25	
60-4 or never	589 (33.2)	10 (1.7)	1.00			1.00		

Model 1: Adjusted for age at examination and sex. Model 2: Additionally adjusted for childhood and adulthood SEP.

Table 3. Odds ratios (ORs) for composite CKD measure by age first overweight (n = 1512). Restricted to study participants non-missing for childhood and adulthood SEP.

Age first overweight (years)	n (%) of total first overweight at this age	n (%) of those first overweight at this age with composite CKD measure	Model 1			Model 2		
			OR	95 % CI	*P* for trend	OR	95 % CI	*P* for trend
26	264 (17.5)	25 (9.5)	2.68	1.44, 4.96		2.43	1.30, 4.56	
36	216 (14.3)	23 (10.6)	3.06	1.62, 5.76		3.10	1.63, 5.89	
43	212 (14.0)	10 (4.7)	1.23	0.56, 2.68	<0.001	1.25	0.57, 2.73	<0.001
53	306 (20.2)	11 (3.6)	0.94	0.44, 1.98		0.95	0.45, 2.01	
60-4 or never	514 (34.0)	20 (3.9)	1.00			1.00		

Model 1: Adjusted for age at examination and sex. Model 2: Additionally adjusted for childhood and adulthood SEP.

Table 4. Odds ratios (ORs) for estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 by overweight status in the multiple imputation analysis (n = 4584).

Overweight	%[A] of total who are overweight	%[A] of non-overweight with eGFR < 60 ml/min/1.73m^2	%[A] of overweight with eGFR < 60 ml/min/1.73m^2	Model 1		Model 2	
				OR	95 % CI	OR	95 % CI
Creatinine-based eGFR							
Age 20	12.6	3.6	4.0	1.12	0.60, 2.10	1.07	0.57, 2.01
Age 26	21.0	3.3	4.7	1.42	0.87, 2.34	1.37	0.82, 2.27
Age 36	35.9	2.8	5.0	1.83	1.16, 2.90	1.77	1.12, 2.81
Age 43	49.0	2.7	4.5	1.67	1.08, 2.58	1.62	1.05, 2.51
Age 53	66.4	2.6	4.1	1.60	0.95, 2.70	1.57	0.93, 2.64
Age 60-4	72.7	2.2	4.2	1.95	1.06, 3.58	1.90	1.02, 3.53
Cystatin C-based eGFR							
Age 20	12.6	2.6	3.9	1.65	0.86, 3.16	1.49	0.77, 2.88
Age 26	21.0	2.5	3.7	1.74	0.96, 3.15	1.57	0.87, 2.86
Age 36	35.9	2.2	3.9	2.35	1.41, 3.91	2.15	1.29, 3.56
Age 43	49.0	2.0	3.6	2.15	1.28, 3.61	2.00	1.19, 3.36
Age 53	66.4	1.9	3.2	2.09	1.14, 3.82	1.97	1.08, 3.59
Age 60-4	72.7	1.7	3.2	2.19	1.08, 4.47	2.04	1.01, 4.13

[A]Average across all 50 imputed datasets.

Model 1: Adjusted for age at examination and sex. Model 2: Additionally adjusted for childhood and adulthood SEP.

Table 5. Odds ratios (ORs) for urine albumin-creatinine ratio (UACR) ≥ 3.5mg/mmol by overweight status in the multiple imputation analysis (n = 4584).

Overweight	%[A] of total who are overweight	%[A] of non-overweight with UACR ≥ 3.5mg/mmol	%[A] of overweight with UACR ≥ 3.5mg/mmol	Model 1		Model 2	
				OR	95 % CI	OR	95 % CI
Age 20	12.6	2.7	3.7	1.30	0.67, 2.54	1.29	0.66, 2.52
Age 26	21.0	2.6	3.8	1.41	0.86, 2.31	1.39	0.84, 2.31
Age 36	35.9	2.2	3.9	1.67	1.07, 2.60	1.65	1.05, 2.59
Age 43	49.0	2.4	3.3	1.34	0.85, 2.13	1.32	0.83, 2.10
Age 53	66.4	2.2	3.1	1.36	0.82, 2.26	1.33	0.80, 2.22
Age 60-4	72.7	2.6	2.9	1.07	0.65, 1.78	1.05	0.63, 1.75

[A]Average across all 50 imputed datasets.

Model 1: Adjusted for age at examination and sex. Model 2: Additionally adjusted for childhood and adulthood SEP.

Table 6. Odds ratios (ORs) for composite CKD measure by overweight status in the multiple imputation analysis (n = 4584).

Overweight	%[A] of total who are overweight	%[A] of non-overweight with composite CKD measure	%[A] of overweight with composite CKD measure	Model 1		Model 2	
				OR	95 % CI	OR	95 % CI
Age 20	12.6	7.8	10.4	1.38	0.94, 2.04	1.31	0.89, 1.95
Age 26	21.0	7.5	10.6	1.50	1.07, 2.11	1.43	1.00, 2.04
Age 36	35.9	6.4	11.2	1.92	1.46, 2.54	1.84	1.40, 2.44
Age 43	49.0	6.4	9.9	1.64	1.23, 2.20	1.58	1.18, 2.12
Age 53	66.4	6.3	9.1	1.54	1.11, 2.15	1.49	1.07, 2.09
Age 60-4	72.7	5.9	9.0	1.58	1.06, 2.36	1.52	1.02, 2.28

[A]Average across all 50 imputed datasets.

Model 1: Adjusted for age at examination and sex. Model 2: Additionally adjusted for childhood and adulthood SEP.

Table 7. Odds ratios (ORs) for estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 by overweight status. Restricted to study participants non-missing for childhood and adulthood SEP.

Overweight	n	n (%) of total who are overweight	n (%) of non-overweight with eGFR < 60 ml/min/1.73m^2	n (%) of overweight with eGFR < 60 ml/min/1.73m^2	Model 1		Model 2	
					OR	95 % CI	OR	95 % CI
Creatinine-based eGFR								
Age 20	1371	163 (11.9)	24 (2.0)	4 (2.5)	1.31	0.45, 3.83	1.07	0.36, 3.21
Age 26	1471	270 (18.4)	22 (1.8)	8 (3.0)	1.80	0.78, 4.12	1.48	0.64, 3.46
Age 36	1508	472 (31.3)	16 (1.5)	17 (3.6)	2.80	1.38, 5.69	2.59	1.25, 5.35
Age 43	1558	695 (44.6)	13 (1.5)	20 (2.9)	2.10	1.03, 4.30	2.00	0.97, 4.12
Age 53	1622	1059 (65.3)	8 (1.4)	25 (2.4)	1.84	0.82, 4.14	1.83	0.81, 4.14
Age 60-4	1617	1125 (69.6)	5 (1.0)	29 (2.6)	2.71	1.04, 7.08	2.55	0.97, 6.70
Cystatin C-based eGFR								
Age 20	1510	178 (11.8)	29 (2.2)	8 (4.5)	2.36	1.05, 5.29	1.88	0.82, 4.30
Age 26	1614	295 (18.3)	26 (2.0)	10 (3.4)	2.11	1.00, 4.48	1.64	0.76, 3.54
Age 36	1661	522 (31.4)	17 (1.5)	20 (3.8)	3.51	1.79, 6.86	3.09	1.56, 6.13
Age 43	1715	767 (44.7)	13 (1.4)	25 (3.3)	3.02	1.52, 6.00	2.78	1.39, 5.55
Age 53	1783	1174 (65.8)	8 (1.3)	32 (2.7)	2.48	1.13, 5.44	2.34	1.06, 5.16
Age 60-4	1775	1245 (70.1)	6 (1.1)	34 (2.7)	2.74	1.14, 6.59	2.42	1.00, 5.85

Model 1: Adjusted for age at examination and sex. Model 2: Additionally adjusted for childhood and adulthood SEP.

Table 8. Odds ratios (ORs) for urine albumin-creatinine ratio (UACR) ≥ 3.5mg/mmol by overweight status. Restricted to study participants non-missing for childhood and adulthood SEP.

Overweight	n	n (%) of total who are overweight	n (%) of non-overweight with UACR ≥ 3.5mg/mmol	n (%) of overweight with UACR ≥ 3.5mg/mmol	Model 1		Model 2	
					OR	95 % CI	OR	95 % CI
Age 20	1595	186 (11.7)	38 (2.7)	7 (3.8)	1.32	0.58, 3.00	1.29	0.56, 2.97
Age 26	1704	312 (18.3)	38 (2.7)	15 (4.8)	1.62	0.87, 3.00	1.61	0.86, 3.01
Age 36	1746	560 (32.1)	25 (2.1)	27 (4.8)	2.05	1.16, 3.60	2.02	1.14, 3.58
Age 43	1806	815 (45.1)	23 (2.3)	29 (3.6)	1.37	0.78, 3.40	1.34	0.76, 2.36
Age 53	1879	1242 (66.1)	13 (2.0)	40 (3.2)	1.44	0.76, 2.73	1.39	0.73, 2.63
Age 60-4	1870	1322 (70.7)	14 (2.6)	37 (2.8)	1.03	0.55, 1.92	0.98	0.52, 1.85

Model 1: Adjusted for age at examination and sex. Model 2: Additionally adjusted for childhood and adulthood SEP.

Table 9. Odds ratios (ORs) for composite CKD measure by overweight status. Restricted to study participants non-missing for childhood and adulthood SEP.

Overweight	n	n (%) of total who are overweight	n (%) of non-overweight with composite CKD measure	n (%) of overweight with composite CKD measure	Model 1		Model 2	
					OR	95 % CI	OR	95 % CI
Age 20	1354	162 (12.0)	63 (5.3)	15 (9.3)	1.85	1.02, 3.33	1.60	0.87, 2.92
Age 26	1451	264 (18.2)	62 (5.2)	25 (9.5)	1.90	1.16, 3.10	1.65	1.00, 2.73
Age 36	1487	462 (31.1)	42 (4.1)	47 (10.2)	2.73	1.75, 4.25	2.56	1.63, 4.01
Age 43	1536	683 (44.5)	38 (4.5)	52 (7.6)	1.76	1.13, 2.72	1.68	1.08, 2.62
Age 53	1601	1043 (65.1)	25 (4.5)	68 (6.5)	1.50	0.94, 2.41	1.46	0.90, 2.36
Age 60-4	1595	1106 (69.3)	22 (4.5)	69 (6.2)	1.41	0.86, 2.31	1.34	0.81, 2.20

Model 1: Adjusted for age at examination and sex. Model 2: Additionally adjusted for childhood and adulthood SEP.