

Serum urea concentration and risk of 16 site-specific cancers, overall cancer, and cancer mortality in individuals with metabolic syndrome: a cohort study

E Wu et al.

Supplementary material content

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Supplementary Tables

Table S1 Criteria for clinical diagnosis of the metabolic syndrome

Factors	Definition
Abdominal obesity	measured by waist circumference thresholds that are ethnic and gender-group specific
High BP	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg, or lower hypertension therapy
Elevated FG	FG ≥ 100 mg/dL, or drug therapy to reduce elevated FG, or glucose ≥ 11.1 mmol/L (200 mg/dL) or HbA1c ≥ 48 mmol/mol (6.5%) captured hyperglycemia even in the non-fasted state
Lower HDLC	< 40 mg/dL (1.0 mmol/L) in males; < 50 mg/dL (1.3 mmol/L) in females, or drug treatment for reduced HDLC
High TG	≥ 150 mg/dL (1.7 mmol/L), or drug therapy for elevated TG

BP: blood pressure; FG: fasting glucose, HDLC: high-density lipoprotein cholesterol; TG: triglycerides.

Table S2 Coding of outcomes

Outcome	ICD-10	ICD-9
Cause of death		
Cancer mortality	C00-C97	
Cardiovascular diseases mortality	I00-I99	
Respiratory disease	J09-J98	
Digestive system disease	K20-K93	
Overall cancer incidence	C00-C97	140-208
16 site specific cancer types		
Oesophageal	C15	150
Stomach	C16	151
Colorectal	C18-20	153, 1540, 1541
Liver	C22	1550
Pancreas	C25	157
Lung	C34	1622-1629
Breast	C50	174,175
Corpus uteri	C54	182
Prostate	C61	185
Kidney	C64-C65	1890、 1891
Bladder	C67	188
Brain	C71	191
Thyroid	C73	193
Non-Hodgkin lymphoma	C82-C86	2020-2022
Multiple myeloma	C90	2030
Leukaemia	C91-C95	204-208

ICD: International Classification of Diseases.

Table S3 *P*-values for global Schoenfeld residuals test across 16 site-specific cancers, overall cancer incidence, and cancer mortality

Outcome	<i>p</i> -value for global Schoenfeld residuals test
Stomach cancer	0.78
Oesophageal cancer	0.7
Lung cancer	0.16
Colorectal cancer	0.16
Corpus uteri cancer	0.26
Brain cancer	0.68
NHL cancer	0.21
Liver cancer	0.94
Breast cancer	0.83
Pancreatic cancer	0.46
MM cancer	0.64
Bladder cancer	0.14
Leukaemia cancer	0.18
Prostate cancer	0.47
Kidney cancer	0.62
Thyroid cancer	0.92
Overall cancer	0.051
Cancer mortality	0.87

Table S4 HRs (95% CIs) for 16 site-specific cancers, overall cancer and cancer mortality according to serum urea categories

Cancer outcomes	Serum urea concentration, mmol/L						
	Q1 (< 4.59) (<i>n</i> = 27058)	Q2 (4.59-5.38) (<i>n</i> = 27129)	<i>p</i> -value	Q3 (5.39-6.29) (<i>n</i> = 27052)	<i>p</i> -value	Q4 (>6.29) (<i>n</i> = 27045)	<i>p</i> -value
Stomach (<i>n</i> = 234)							
No. of cases	59	54		59		62	
Model 1	1.00 (ref.)	0.78 (0.54-1.13)	0.184	0.75 (0.52-1.09)	0.131	0.68 (0.47-0.98)	0.037
Model 2	1.00 (ref.)	0.79 (0.55-1.15)	0.215	0.77 (0.53-1.11)	0.164	0.68 (0.47-0.99)	0.043
Model 3	1.00 (ref.)	0.79 (0.54-1.15)	0.214	0.77 (0.53-1.11)	0.160	0.67 (0.45-0.98)	0.040
Oesophageal (<i>n</i> = 346)							
No. of cases	91	65		89		101	
Model 1	1.00 (ref.)	0.57 (0.41-0.78)	0.001	0.68 (0.51-0.92)	0.012	0.67 (0.50-0.89)	0.006
Model 2	1.00 (ref.)	0.59 (0.43-0.82)	0.001	0.72 (0.54-0.97)	0.031	0.69 (0.52-0.93)	0.014
Model 3	1.00 (ref.)	0.60 (0.43-0.82)	0.002	0.73 (0.54-0.98)	0.035	0.68 (0.50-0.92)	0.013
Lung (<i>n</i> = 1223)							
No. of cases	322	276		311		314	
Model 1	1.00 (ref.)	0.72 (0.61-0.84)	<0.001	0.72 (0.61-0.84)	<0.001	0.62 (0.53-0.72)	<0.001
Model 2	1.00 (ref.)	0.82 (0.70-0.96)	0.016	0.88 (0.75-1.03)	0.116	0.78 (0.66-0.92)	0.003
Model 3	1.00 (ref.)	0.84 (0.71-0.99)	0.035	0.90 (0.77-1.06)	0.116	0.76 (0.64-0.90)	0.001
Colorectal (<i>n</i> = 1592)							
No. of cases	350	364		412		466	
Model 1	1.00 (ref.)	0.86 (0.74-1.00)	0.050	0.88 (0.76-1.02)	0.079	0.88 (0.76-1.02)	0.079
Model 2	1.00 (ref.)	0.87 (0.75-1.00)	0.054	0.88 (0.76-1.02)	0.087	0.88 (0.76-1.01)	0.073
Model 3	1.00 (ref.)	0.86 (0.74-0.99)	0.045	0.87 (0.75-1.01)	0.063	0.86 (0.74-0.99)	0.048
Corpus uteri (<i>n</i> = 551)	(<i>F.n</i> = 15449)	(<i>F.n</i> = 13702)		(<i>F.n</i> = 12635)		(<i>F.n</i> = 11605)	

	No. of cases	142	137		150		122	
	Model 1	1.00 (ref.)	1.01 (0.79-1.28)	0.960	1.14 (0.90-1.45)	0.274	0.97 (0.75-1.25)	0.814
	Model 2	1.00 (ref.)	1.00 (0.79-1.27)	0.999	1.09 (0.86-1.38)	0.500	0.88 (0.68-1.13)	0.310
	Model 3	1.00 (ref.)	1.00 (0.79-1.27)	0.989	1.08 (0.85-1.37)	0.529	0.88 (0.67-1.15)	0.336
Brain (<i>n</i> = 197)								
	No. of cases	41	61		47		48	
	Model 1	1.00 (ref.)	1.30 (0.88-1.94)	0.193	0.95 (0.62-1.45)	0.807	0.90 (0.59-1.39)	0.639
	Model 2	1.00 (ref.)	1.31 (0.88-1.94)	0.191	0.95 (0.62-1.46)	0.818	0.90 (0.59-1.39)	0.643
	Model 3	1.00 (ref.)	1.30 (0.87-1.95)	0.194	0.95 (0.62-1.46)	0.818	0.89 (0.56-1.39)	0.596
NHL (<i>n</i> = 526)								
	No. of cases	115	120		134		157	
	Model 1	1.00 (ref.)	0.88 (0.68-1.13)	0.314	0.89 (0.69-1.15)	0.361	0.93 (0.73-1.19)	0.575
	Model 2	1.00 (ref.)	0.88 (0.68-1.14)	0.329	0.89 (0.69-1.15)	0.361	0.93 (0.72-1.19)	0.545
	Model 3	1.00 (ref.)	0.88 (0.68-1.14)	0.344	0.89 (0.69-1.15)	0.365	0.89 (0.69-1.16)	0.384
Liver (<i>n</i> = 288)								
	No. of cases	63	62		76		87	
	Model 1	1.00 (ref.)	0.76 (0.53-1.08)	0.128	0.82 (0.59-1.15)	0.254	0.79 (0.56-1.10)	0.156
	Model 2	1.00 (ref.)	0.78 (0.54-1.11)	0.159	0.84 (0.60-1.17)	0.303	0.79 (0.56-1.10)	0.162
	Model 3	1.00 (ref.)	0.84 (0.59-1.20)	0.327	0.95 (0.67-1.34)	0.765	0.91 (0.64-1.32)	0.627
Breast (<i>n</i> = 2139)								
	No. of cases	554	576		523		486	
	Model 1	1.00 (ref.)	1.08 (0.96-1.22)	0.197	1.03 (0.91-1.16)	0.662	1.02 (0.89-1.15)	0.822
	Model 2	1.00 (ref.)	1.08 (0.96-1.22)	0.181	1.03 (0.91-1.17)	0.628	1.02 (0.89-1.16)	0.764
	Model 3	1.00 (ref.)	1.09 (0.97-1.23)	0.156	1.04 (0.92-1.18)	0.549	1.04 (0.91-1.19)	0.574
Pancreas (<i>n</i> = 432)								
	No. of cases	89	108		101		134	

	Model 1	1.00 (ref.)	1.04 (0.78-1.37)	0.805	0.88 (0.66-1.18)	0.401	1.05 (0.80-1.39)	0.716
	Model 2	1.00 (ref.)	1.06 (0.80-1.40)	0.711	0.89 (0.68-1.21)	0.489	1.07 (0.81-1.41)	0.626
	Model 3	1.00 (ref.)	1.07 (0.81-1.42)	0.643	0.91 (0.68-1.21)	0.546	1.06 (0.79-1.42)	0.685
MM ($n = 225$)								
	No. of cases	41	59		60		65	
	Model 1	1.00 (ref.)	1.24 (0.83-1.85)	0.297	1.15 (0.77-1.72)	0.507	1.10 (0.74-1.64)	0.645
	Model 2	1.00 (ref.)	1.24 (0.83-1.84)	0.303	1.15 (0.77-1.72)	0.509	1.11 (0.74-1.66)	0.607
	Model 3	1.00 (ref.)	1.24 (0.83-1.85)	0.303	1.15 (0.77-1.73)	0.494	1.11 (0.73-1.69)	0.622
Bladder ($n = 321$)								
	No. of cases	52	76		91		102	
	Model 1	1.00 (ref.)	1.14 (0.80-1.63)	0.459	1.17 (0.83-1.65)	0.381	1.09 (0.77-1.53)	0.633
	Model 2	1.00 (ref.)	1.20 (0.84-1.71)	0.316	1.25 (0.89-1.76)	0.207	1.17 (0.83-1.65)	0.372
	Model 3	1.00 (ref.)	1.21 (0.85-1.73)	0.295	1.26 (0.89-1.78)	0.191	1.12 (0.78-1.60)	0.542
Leukaemia ($n = 340$)								
	No. of cases	62	86		84		108	
	Model 1	1.00 (ref.)	1.19 (0.86-1.65)	0.306	1.06 (0.76-1.47)	0.754	1.21 (0.88-1.67)	0.242
	Model 2	1.00 (ref.)	1.19 (0.85-1.65)	0.311	1.05 (0.75-1.47)	0.769	1.21 (0.87-1.66)	0.258
	Model 3	1.00 (ref.)	1.19 (0.85-1.65)	0.307	1.05 (0.75-1.47)	0.787	1.15 (0.82-1.62)	0.405
Prostate ($n = 2542$)								
		(M. $n = 11609$)	(M. $n = 13427$)		(M. $n = 14417$)		(M. $n = 15440$)	
	No. of cases	415	583		690		854	
	Model 1	1.00 (ref.)	1.07 (0.94-1.21)	0.299	1.07 (0.95-1.21)	0.285	1.09 (0.96-1.22)	0.178
	Model 2	1.00 (ref.)	1.06 (0.94-1.21)	0.334	1.06 (0.94-1.20)	0.321	1.09 (0.96-1.22)	0.184
	Model 3	1.00 (ref.)	1.06 (0.94-1.21)	0.346	1.08 (0.95-1.22)	0.250	1.15 (1.02-1.30)	0.027
Kidney ($n = 496$)								
	No. of cases	92	104		123		177	
	Model 1	1.00 (ref.)	0.99 (0.75-1.31)	0.936	1.09 (0.83-1.43)	0.542	1.44 (1.11-1.87)	0.006

	Model 2	1.00 (ref.)	0.98 (0.74-1.30)	0.906	1.08 (0.82-1.43)	0.571	1.40 (1.08-1.82)	0.012
	Model 3	1.00 (ref.)	0.98 (0.74-1.30)	0.895	1.06 (0.80-1.40)	0.690	1.24 (0.95-1.63)	0.115
Thyroid (<i>n</i> = 118)								
	No. of cases	32	29		28		29	
	Model 1	1.00 (ref.)	1.05 (0.63-1.74)	0.865	1.10 (0.65-1.85)	0.728	1.24 (0.73-2.12)	0.423
	Model 2	1.00 (ref.)	1.05 (0.63-1.75)	0.843	1.10 (0.65-1.87)	0.711	1.24 (0.73-2.12)	0.432
	Model 3	1.00 (ref.)	1.07 (0.64-1.79)	0.784	1.15 (0.67-1.95)	0.613	1.35 (0.77-2.38)	0.300
Overall cancer incidence (<i>n</i> = 18548)								
	No. of cases	3905	4387		4822		5434	
	Model 1	1.00 (ref.)	0.94 (0.90-0.99)	0.008	0.94 (0.90-0.99)	0.008	0.96 (0.92-0.99)	0.042
	Model 2	1.00 (ref.)	0.95 (0.91-0.99)	0.023	0.96 (0.92-0.99)	0.038	0.97 (0.93-1.01)	0.144
	Model 3	1.00 (ref.)	0.95 (0.91-0.99)	0.020	0.95 (0.91-0.99)	0.023	0.95 (0.91-0.99)	0.020
Cancer mortality (<i>n</i> = 5034)								
	No. of cases	1114	1115		1318		1487	
	Model 1	1.00 (ref.)	0.81 (0.75-0.88)	<0.001	0.85 (0.79-0.92)	<0.001	0.84 (0.78-0.91)	<0.001
	Model 2	1.00 (ref.)	0.84 (0.77-0.91)	<0.001	0.89 (0.82-0.97)	0.004	0.88 (0.81-0.95)	0.001
	Model 3	1.00 (ref.)	0.84 (0.78-0.92)	<0.001	0.89 (0.82-0.97)	0.005	0.83 (0.77-0.91)	<0.001

Cox proportional hazards regression models adjusted for age at recruitment, sex, ethnicity, education, and TDI in Model 1; Model 2: adjusted for model one and BMI, smoking, diet, sleep duration, frequency of alcohol intake and physical activity; Model 3: adjusted for model two and hypertension medication, cholesterol-lowering medications, insulin, creatinine, cystatin C, glucose, HbA1c, TG and overall health rating. Female corpus uteri and male prostate cancers were not adjusted for sex due to their sex-specificity. *F.n*, number of female. *M.n*, number of male. NHL, non-Hodgkin lymphoma. MM, Multiple myeloma.

Table S5 HR (95% CI) of serum urea concentrations with risk of overall cancer incidence and cancer mortality stratified by baseline characteristics

Subgroup	Cancer Cases	Overall cancer incidence risk				<i>p for</i>	Mortality Cases	Cancer mortality risk				<i>p for</i>
		Q1 of urea	Q2 of urea	Q3 of urea	Q4 of urea	interaction		Q1 of urea	Q2 of urea	Q3 of urea	Q4 of urea	interaction
Age						<0.001						<0.001
< 60 years	6220	1.00 (ref)	0.95 (0.89-1.02)	0.97 (0.90-1.04)	0.92 (0.85-0.99)		1434	1.00 (ref)	0.85 (0.74-0.98)	0.99 (0.86-1.15)	0.90 (0.77-1.05)	
≥ 60 years	12328	1.00 (ref)	0.95 (0.90-1.01)	0.95 (0.90-1.01)	0.97 (0.92-1.03)		3600	1.00 (ref)	0.84 (0.76-0.93)	0.86 (0.78-0.95)	0.82 (0.74-0.90)	
Sex						<0.001						<0.001
Female	8253	1.00 (ref)	1.00 (0.94-1.06)	0.96 (0.90-1.02)	0.94 (0.88-1.00)		2129	1.00 (ref)	0.86 (0.76-0.97)	0.89 (0.79-1.01)	0.88 (0.77-0.99)	
Male	10295	1.00 (ref)	0.93 (0.88-0.99)	0.97 (0.92-1.03)	0.97 (0.91-1.03)		2905	1.00 (ref)	0.85 (0.76-0.95)	0.91 (0.81-1.01)	0.81 (0.73-0.91)	
Education						0.012						0.001
Higher	4175	1.00 (ref)	0.95 (0.86-1.03)	0.95 (0.87-1.04)	0.96 (0.88-1.05)		981	1.00 (ref)	0.77 (0.64-0.93)	0.94 (0.79-1.13)	0.85 (0.70-1.03)	
Others	14373	1.00 (ref)	0.95 (0.91-1.00)	0.95 (0.91-1.00)	0.95 (0.90-0.99)		4053	1.00 (ref)	0.87 (0.79-0.95)	0.89 (0.81-0.98)	0.84 (0.76-0.92)	
TDI						0.004						0.001
Lowest quintile	3973	1.00 (ref)	0.97 (0.88-1.07)	0.94 (0.86-1.04)	0.93 (0.85-1.03)		918	1.00 (ref)	0.91 (0.75-1.12)	0.90 (0.74-1.10)	0.83 (0.67-1.02)	
Quintile 2-4th	11149	1.00 (ref)	0.96 (0.91-1.02)	0.96 (0.91-1.02)	0.98 (0.92-1.03)		2973	1.00 (ref)	0.80 (0.72-0.90)	0.91 (0.81-1.01)	0.84 (0.75-0.94)	
Highest quintile	3426	1.00 (ref)	0.89 (0.81-0.98)	0.94 (0.85-1.03)	0.89 (0.81-0.99)		1143	1.00 (ref)	0.92 (0.78-1.08)	0.89 (0.75-1.05)	0.84 (0.71-0.99)	
BMI						0.011						0.001
< 25 kg/m ²	972	1.00 (ref)	0.95 (0.79-1.15)	1.06 (0.88-1.27)	1.04 (0.86-1.25)		267	1.00 (ref)	0.91 (0.64-1.30)	1.12 (0.79-1.58)	1.00 (0.70-1.42)	
25-29.9 kg/m ²	6994	1.00 (ref)	0.98 (0.91-1.06)	0.96 (0.90-1.04)	1.01 (0.94-1.08)		1840	1.00 (ref)	0.95 (0.83-1.09)	0.93 (0.81-1.07)	0.84 (0.73-0.97)	
≥ 30 kg/m ²	10582	1.00 (ref)	0.93 (0.88-0.99)	0.94 (0.89-0.99)	0.91 (0.86-0.97)		2927	1.00 (ref)	0.79 (0.70-0.88)	0.88 (0.79-0.98)	0.84 (0.75-0.94)	
Smoking status						<0.001						<0.001
Never	8097	1.00 (ref)	0.98 (0.92-1.05)	0.99 (0.93-1.06)	0.98 (0.92-1.05)		1771	1.00 (ref)	0.82 (0.71-0.95)	0.89 (0.78-1.02)	0.87 (0.76-1.01)	
Previous	8073	1.00 (ref)	0.94 (0.88-1.01)	0.92 (0.87-0.99)	0.95 (0.89-1.02)		2310	1.00 (ref)	0.90 (0.79-1.02)	0.92 (0.81-1.04)	0.86 (0.76-0.98)	
Current	2378	1.00 (ref)	0.91 (0.82-1.02)	0.94 (0.84-1.06)	0.88 (0.78-0.99)		953	1.00 (ref)	0.82 (0.69-0.98)	0.94 (0.79-1.12)	0.77 (0.63-0.93)	
Alcohol consumption						0.162						0.003
Low	4709	1.00 (ref)	0.93 (0.85-1.01)	0.95 (0.87-1.03)	0.98 (0.90-1.07)		1464	1.00 (ref)	0.86 (0.73-1.00)	1.06 (0.92-1.24)	0.93 (0.79-1.08)	
Moderate	6997	1.00 (ref)	0.95 (0.88-1.02)	0.96 (0.89-1.03)	0.93 (0.86-0.99)		1823	1.00 (ref)	0.93 (0.81-1.07)	0.88 (0.77-1.01)	0.83 (0.72-0.96)	

High	6842	1.00 (ref)	0.97 (0.90-1.04)	0.95 (0.88-1.02)	0.95 (0.88-1.02)		1747	1.00 (ref)	0.76 (0.66-0.88)	0.81 (0.71-0.93)	0.79 (0.68-0.91)	
Diet						0.014						<0.001
Unhealthy	10353	1.00 (ref)	0.91 (0.86-0.97)	0.95 (0.90-1.01)	0.91 (0.86-0.97)		2933	1.00 (ref)	0.86 (0.77-0.96)	0.91 (0.82-1.02)	0.81 (0.72-0.90)	
Healthy	8195	1.00 (ref)	1.00 (0.94-1.07)	0.95 (0.89-1.02)	1.00 (0.93-1.07)		2101	1.00 (ref)	0.83 (0.73-0.95)	0.88 (0.78-0.99)	0.88 (0.77-1.00)	
Cholesterol-lowering						0.0539						0.006
No	11720	1.00 (ref)	0.96 (0.91-1.01)	0.96 (0.91-1.02)	0.98 (0.93-1.04)		2992	1.00 (ref)	0.84 (0.75-0.93)	0.89 (0.81-0.99)	0.86 (0.77-0.96)	
Yes	6828	1.00 (ref)	0.92 (0.85-0.99)	0.92 (0.86-0.99)	0.90 (0.84-0.97)		2042	1.00 (ref)	0.87 (0.75-0.99)	0.90 (0.79-1.03)	0.81 (0.71-0.93)	
Antihypertensive drug						0.002						0.004
No	10516	1.00 (ref)	0.95 (0.90-1.01)	0.92 (0.87-0.97)	0.97 (0.92-1.03)		2689	1.00 (ref)	0.83 (0.74-0.92)	0.83 (0.74-0.92)	0.83 (0.74-0.93)	
Yes	8032	1.00 (ref)	0.94 (0.88-1.01)	0.99 (0.92-1.06)	0.94 (0.87-1.00)		2345	1.00 (ref)	0.87 (0.76-0.99)	0.98 (0.86-1.11)	0.86 (0.76-0.98)	
Insulin						0.118						<0.001
No	17931	1.00 (ref)	0.95 (0.91-0.99)	0.95 (0.91-0.99)	0.95 (0.91-0.99)		4809	1.00 (ref)	0.84 (0.78-0.92)	0.90 (0.83-0.98)	0.82 (0.76-0.90)	
Yes	617	1.00 (ref)	0.96 (0.74-1.25)	0.76 (0.58-0.99)	0.94 (0.73-1.20)		225	1.00 (ref)	0.83 (0.53-1.31)	0.72 (0.46-1.14)	1.02 (0.68-1.54)	
Sleep duration						0.042						0.002
< 7	4643	1.00 (ref)	1.00 (0.91-1.09)	0.98 (0.90-1.07)	0.99 (0.91-1.08)		1365	1.00 (ref)	0.91 (0.77-1.07)	0.98(0.84-1.14)	0.93 (0.79-1.09)	
7-8	11798	1.00 (ref)	0.93 (0.88-0.98)	0.95 (0.90-0.99)	0.93 (0.88-0.99)		3030	1.00 (ref)	0.80 (0.72-0.89)	0.86 (0.78-0.96)	0.79 (0.71-0.89)	
> 8	2107	1.00 (ref)	0.98 (0.86-1.12)	0.92 (0.81-1.06)	0.96 (0.84-1.09)		639	1.00 (ref)	1.00 (0.78-1.27)	0.93 (0.73-1.18)	0.88 (0.69-1.13)	

Cox proportional hazards regression models adjusted for age at recruitment, sex, ethnicity, education, TDI, BMI, smoking, diet, sleep duration, frequency of alcohol intake, physical activity, hypertension medication, cholesterol-lowering medications, insulin, creatinine, cystatin C, glucose, HbA1c, TG and overall health rating.

Table S6 HR (95% CI) of serum urea concentration with risk of 16 site-specific cancers, overall cancer incidence, and cancer mortality when the participants were limited to white ethnicity background ($n=99,901$)

Endpoints	No. of Cases	Quartiles of serum urea concentration, mmol/L						
		Q1 (<4.59)	Q2 (4.59-5.38)	<i>p</i> -value	Q3 (5.39-6.29)	<i>p</i> -value	Q4 (>6.29)	<i>p</i> -value
Oesophageal	341	1.00 (ref.)	0.60 (0.44-0.83)	0.002	0.72 (0.53-0.98)	0.035	0.68 (0.50-0.92)	0.013
Stomach	218	1.00 (ref.)	0.83 (0.56-1.22)	0.336	0.80 (0.54-1.18)	0.254	0.71 (0.47-1.07)	0.099
Colorectal	1531	1.00 (ref.)	0.85 (0.73-0.99)	0.036	0.84 (0.73-0.98)	0.026	0.83 (0.71-0.97)	0.019
Liver	275	1.00 (ref.)	0.86 (0.59-1.24)	0.417	0.93 (0.65-1.34)	0.705	0.95 (0.66-1.37)	0.780
Pancreas	409	1.00 (ref.)	1.03 (0.77-1.38)	0.843	0.88 (0.65-1.19)	0.405	1.02 (0.75-1.38)	0.905
Lung	1185	1.00 (ref.)	0.84 (0.71-0.99)	0.038	0.91 (0.77-1.07)	0.233	0.75 (0.63-0.89)	0.001
Breast	2029	1.00 (ref.)	1.10 (0.98-1.25)	0.118	1.02 (0.90-1.16)	0.722	1.03 (0.89-1.18)	0.732
Corpus uter	508	1.00 (ref.)	0.94 (0.73-1.20)	0.601	1.04 (0.81-1.33)	0.781	0.86 (0.65-1.13)	0.287
Prostate	2386	1.00 (ref.)	1.05 (0.92-1.20)	0.450	1.05 (0.92-1.20)	0.448	1.15 (1.01-1.30)	0.042
Kidney	473	1.00 (ref.)	0.93 (0.69-1.24)	0.615	1.08 (0.81-1.43)	0.607	1.23 (0.93-1.63)	0.146
Bladder	311	1.00 (ref.)	1.18 (0.82-1.69)	0.375	1.23 (0.86-1.75)	0.262	1.09 (0.76-1.57)	0.631
Brain	188	1.00 (ref.)	1.29 (0.86-1.94)	0.217	0.90 (0.58-1.40)	0.633	0.78 (0.49-1.24)	0.291
Thyroid	105	1.00 (ref.)	1.08 (0.63-1.85)	0.792	1.15 (0.66-2.01)	0.619	1.16 (0.63-2.13)	0.644
Non-Hodgkin lymphoma	502	1.00 (ref.)	0.85 (0.65-1.10)	0.214	0.85 (0.66-1.11)	0.229	0.83 (0.64-1.08)	0.169
Multiple myeloma	204	1.00 (ref.)	1.20 (0.78-1.84)	0.409	1.10 (0.71-1.70)	0.661	1.13 (0.72-1.77)	0.588
Leukaemia	320	1.00 (ref.)	1.12 (0.79-1.57)	0.530	1.00 (0.71-1.41)	0.992	1.08 (0.75-1.51)	0.715
Overall cancer incidence	17859	1.00 (ref.)	0.94 (0.90-0.99)	0.009	0.94 (0.90-0.98)	0.007	0.94 (0.90-0.98)	0.007
Cancer mortality	4848	1.00 (ref.)	0.84 (0.77-0.92)	<0.001	0.89 (0.82-0.96)	0.005	0.83 (0.76-0.91)	<0.001

Cox proportional hazards regression models adjusted for age at recruitment, sex, ethnicity, education, TDI, BMI, smoking, diet, sleep duration, frequency of alcohol intake, physical activity, hypertension medication, cholesterol-lowering medications, insulin, creatinine, cystatin C, glucose, HbA1c, TG and overall health rating. Female corpus uteri and male prostate cancers were not adjusted for sex due to their sex-specificity.

Table S7 HR (95% CI) of serum urea concentration with risk of 16 site-specific cancers, overall cancer incidence, and cancer mortality when excluded the participants developed cancer or died within 2 years of follow-up (n=105,723)

endpoints	No. of Cases	Quartiles of serum urea concentration, mmol/L						
		Q1 (<4.59)	Q2 (4.59-5.38)	p-value	Q3 (5.39-6.29)	p-value	Q4 (>6.29)	p-value
Oesophageal	318	1.00 (ref.)	0.59 (0.42-0.82)	0.002	0.68 (0.50-0.93)	0.015	0.65 (0.47-0.89)	0.007
Stomach	206	1.00 (ref.)	0.79 (0.53-1.18)	0.187	0.77 (0.51-1.14)	0.187	0.71 (0.47-1.07)	0.101
Colorectal	1379	1.00 (ref.)	0.89 (0.76-1.04)	0.147	0.86 (0.74-1.01)	0.060	0.83 (0.71-0.98)	0.025
Liver	268	1.00 (ref.)	0.93 (0.64-1.35)	0.703	0.99 (0.69-1.42)	0.960	0.97 (0.66-1.41)	0.853
Pancreas	393	1.00 (ref.)	1.11 (0.83-1.49)	0.492	0.95 (0.70-1.28)	0.714	1.01 (0.74-1.37)	0.963
Lung	1096	1.00 (ref.)	0.85 (0.72-1.01)	0.057	0.88 (0.74-1.04)	0.140	0.74 (0.62-0.89)	0.001
Breast	1792	1.00 (ref.)	1.15 (1.01-1.31)	0.038	1.07 (0.93-1.22)	0.357	1.05 (0.91-1.22)	0.494
Corpus uter	470	1.00 (ref.)	1.03 (0.79-1.33)	0.843	1.17 (0.90-1.51)	0.239	0.87 (0.65-1.17)	0.372
Prostate	2202	1.00 (ref.)	1.07 (0.93-1.22)	0.353	1.09 (0.95-1.24)	0.214	1.16 (1.01-1.33)	0.030
Kidney	442	1.00 (ref.)	1.06 (0.78-1.43)	0.715	1.09 (0.81-1.46)	0.578	1.29 (0.97-1.73)	0.085
Bladder	277	1.00 (ref.)	1.33 (0.91-1.94)	0.146	1.30 (0.89-1.90)	0.168	1.12 (0.76-1.65)	0.582
Brain	173	1.00 (ref.)	1.35 (0.88-2.06)	0.167	0.86 (0.54-1.38)	0.537	0.89 (0.55-1.44)	0.634
Thyroid	102	1.00 (ref.)	1.25 (0.72-2.17)	0.438	1.25 (0.70-2.24)	0.444	1.38 (0.74-2.56)	0.314
Non-Hodgkin lymphoma	450	1.00 (ref.)	0.82 (0.62-1.08)	0.154	0.83 (0.63-1.09)	0.178	0.84 (0.64-1.11)	0.230
Multiple myeloma	207	1.00 (ref.)	1.25 (0.83-1.89)	0.285	1.05 (0.69-1.61)	0.824	1.08 (0.70-1.67)	0.732
Leukaemia	298	1.00 (ref.)	1.15 (0.82-1.62)	0.432	1.00 (0.70-1.42)	0.998	1.00 (0.69-1.43)	0.980
Overall cancer incidence	16307	1.00 (ref.)	0.96 (0.92-1.01)	0.090	0.95 (0.91-0.99)	0.023	0.94 (0.89-0.98)	0.006
Cancer mortality	4365	1.00 (ref.)	0.86 (0.79-0.94)	0.001	0.88 (0.81-0.96)	0.005	0.82 (0.75-0.90)	<0.001

Cox proportional hazards regression models adjusted for age at recruitment, sex, ethnicity, education, TDI, BMI, smoking, diet, sleep duration, frequency of alcohol intake, physical activity, hypertension medication, cholesterol-lowering medications, insulin, creatinine, cystatin C, glucose, HbA1c, TG and overall health rating. Corpus uteri and prostate cancer were studied in female and male participants, respectively. The sex factor was not adjusted for in the analyses of female corpus uteri and male prostate cancer.

Table S8 HRs (95%CI) for all-cause and cause-specific mortality among patients with MetS according to serum urea quartiles

Endpoints	No. of Mortality	Q1(<4.59) (n = 27058)	Q2(4.59-5.38) (n = 27129)	p-value	Q3 (5.39-6.29) (n = 27052)	p-value	Q4 (>6.29) (n = 27045)	p-value	p-trend
All-cause mortality	12400	1.00 (ref.)	0.80 (0.76-0.85)	<0.001	0.82 (0.78-0.97)	<0.001	0.87 (0.82-0.91)	<0.001	<0.001
Cause-specific mortality									
Cancer mortality	5034	1.00 (ref.)	0.84 (0.78-0.92)	<0.001	0.89 (0.82-0.97)	0.005	0.83 (0.77-0.91)	<0.001	<0.001
CVD mortality	3304	1.00 (ref.)	0.83 (0.74-0.93)	0.001	0.83 (0.74-0.92)	0.001	1.05 (0.95-1.16)	0.374	<0.001
Respiratory disease	918	1.00 (ref.)	0.64 (0.52-.078)	<0.001	0.74 (0.61-0.89)	0.002	0.71 (0.59-0.86)	<0.001	<0.001
Digestive system disease	574	1.00 (ref.)	0.59 (0.46-0.75)	<0.001	0.57 (0.45-0.82)	<0.001	0.56 (0.44-0.72)	<0.001	<0.001
Other mortality	2570	1.00 (ref.)	0.82 (0.72-0.92)	0.001	0.78 (0.69-0.88)	<0.001	0.88 (0.78-0.99)	0.027	<0.001

Cox proportional hazards regression models adjusted for age at recruitment, sex, ethnicity, education, TDI, BMI, smoking, diet, sleep duration, frequency of alcohol intake, physical activity, hypertension medication, cholesterol-lowering medications, insulin, creatinine, cystatin C, glucose, HbA1c, TG and overall health rating.

Table S9 Characteristics of participants with or without MetS at recruitment

	Total (n=424084)	MetS at recruitment		<i>p</i> -value
		No (n=315800)	Yes (n=108284)	
Urea, mean (SD), mmol/L	5.4 (1.4)	5.3 (1.3)	5.6 (1.5)	<0.001
Oesophageal cancer	951	605 (0.20)	346 (0.3)	<0.001
Stomach cancer	645	411 (0.1)	234 (0.2)	<0.001
Colorectal cancer	5095	3503 (1.1)	1592 (1.5)	<0.001
Liver cancer	616	328 (0.1)	288 (0.3)	<0.001
Pancreas cancer	1227	795 (0.3)	432 (0.4)	<0.001
Lung cancer	3625	2402 (0.8)	1223 (1.1)	<0.001
Breast cancer	8062	5923 (1.9)	2139 (2.0)	0.038
Corpus uter cancer	1313	762 (0.2)	551 (0.5)	<0.001
Prostate cancer	9684	7142 (2.3)	2542 (2.3)	0.102
Kidney cancer	1284	788 (0.2)	496 (0.5)	<0.001
Bladder cancer	957	636 (0.2)	321 (0.3)	<0.001
Brain cancer	767	570 (0.2)	197 (0.2)	0.924
Thyroid cancer	377	259 (0.1)	118 (0.1)	0.01
Non-Hodgkin lymphoma cancer	1845	1319 (0.4)	526 (0.5)	0.003
Multiple myeloma cancer	777	552 (0.2)	225 (0.2)	0.028
Leukaemia cancer	1069	729 (0.2)	340 (0.3)	<0.001
Overall cancer incidence	66232	47684 (15.1)	18548 (17.1)	<0.001
Cancer mortality	14922	9888 (3.1)	5034 (4.6)	<0.001

Pearson's χ^2 test was conducted to analyze unordered categorical variables, Student's *t*-test was examined for normally distributed data.

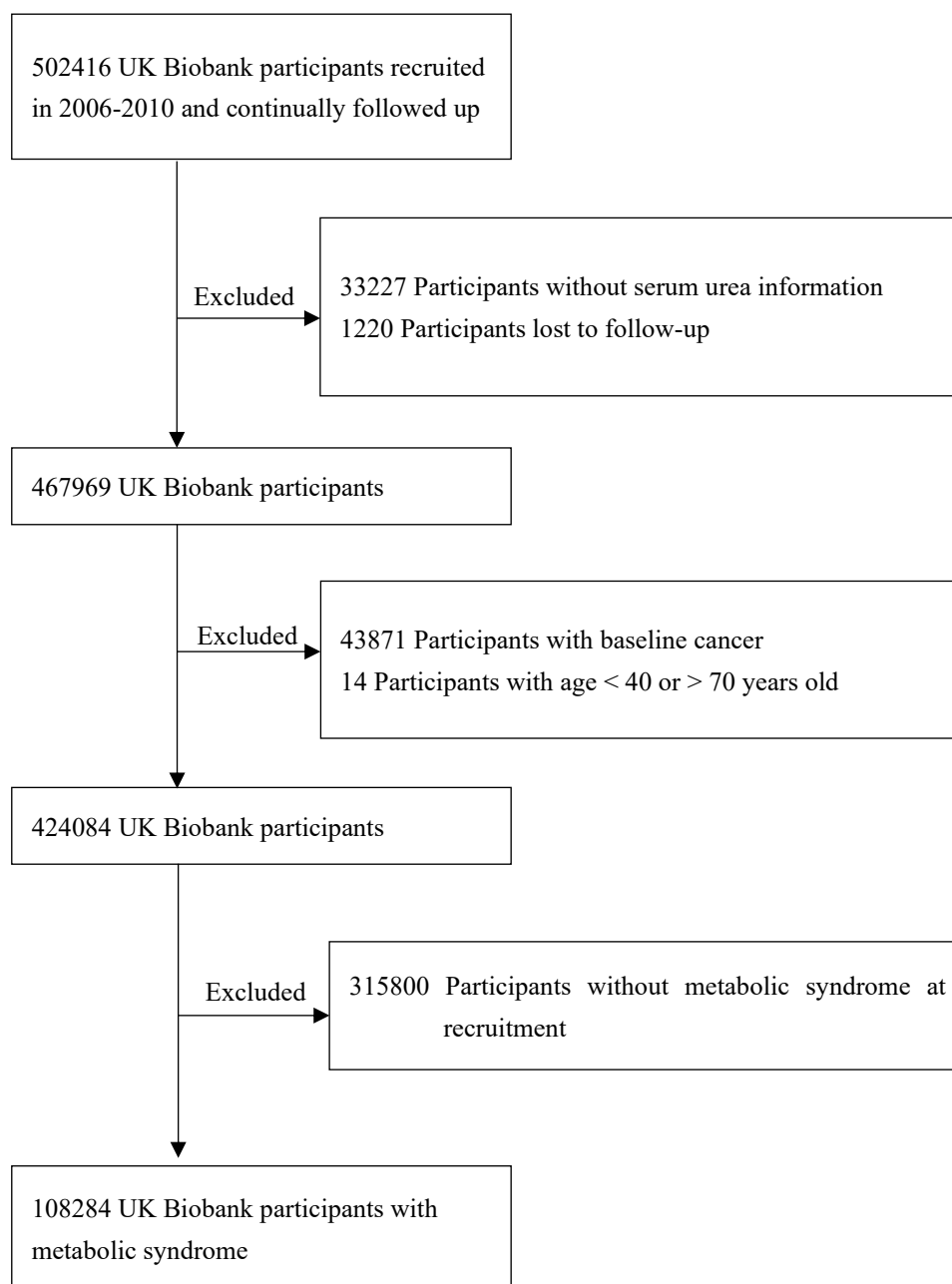
The column percentages for the binary variable sum to 100, and present the percentages of the “yes” option.

Table S10 HR (95% CI) of serum urea concentration with risk of 16 site-specific cancers, overall cancer incidence, and cancer mortality when the study was limited to participants without MetS at recruitment ($n = 315,800$)

Endpoints	No. of Cases	Quartiles of serum urea concentration, mmol/L						
		Q1 (< 4.45)	Q2 (4.45-5.21)	<i>p</i> -value	Q3 (5.22-6.07)	<i>p</i> -value	Q4 (> 6.07)	<i>p</i> -value
Oesophageal cancer	605	1.00 (ref.)	0.78 (0.62-0.99)	0.040	0.76 (0.60-0.96)	0.020	0.65 (0.51-0.83)	<0.001
Stomach cancer	411	1.00 (ref.)	1.03 (0.76-1.39)	0.859	1.09 (0.81-1.46)	0.570	0.89 (0.66-1.21)	0.468
Colorectal cancer	3503	1.00 (ref.)	0.89 (0.81-0.99)	0.024	0.76 (0.68-0.83)	<0.001	0.78 (0.71-0.86)	<0.001
Liver cancer	328	1.00 (ref.)	0.86 (0.63-1.17)	0.327	0.68 (0.49-0.94)	0.018	0.81 (0.59-1.12)	0.202
Pancreas cancer	795	1.00 (ref.)	0.76 (0.61-0.94)	0.010	0.94 (0.76-1.15)	0.523	0.86 (0.70-1.07)	0.173
Lung cancer	2402	1.00 (ref.)	0.83 (0.74-0.93)	0.001	0.81 (0.72-0.91)	<0.001	0.74 (0.66-0.84)	<0.001
Breast cancer	5923	1.00 (ref.)	0.96 (0.89-1.03)	0.205	0.86 (0.80-0.93)	<0.001	0.89 (0.82-0.96)	0.004
Corpus uter cancer	762	1.00 (ref.)	1.15 (0.93-1.41)	0.205	1.31 (1.06-1.62)	0.012	1.31 (1.05-1.64)	0.019
Prostate cancer	7142	1.00 (ref.)	1.13 (1.05-1.22)	0.002	1.19 (1.11-1.28)	<0.001	1.27 (1.18-1.37)	<0.001
Kidney cancer	788	1.00 (ref.)	0.97 (0.77-1.22)	0.797	1.13 (0.91-1.41)	0.277	1.27 (1.02-1.57)	0.033
Bladder cancer	636	1.00 (ref.)	1.08 (0.83-1.41)	0.584	1.29 (1.01-1.67)	0.047	1.45 (1.13-1.87)	0.004
Brain cancer	570	1.00 (ref.)	1.01 (0.78-1.29)	0.981	1.01 (0.78-1.30)	0.948	1.17 (0.91-1.52)	0.209
Thyroid cancer	259	1.00 (ref.)	0.97 (0.68-1.39)	0.877	1.02 (0.71-1.47)	0.911	1.34 (0.94-1.92)	0.106
Non-Hodgkin lymphoma cancer	1319	1.00 (ref.)	1.12 (0.96-1.32)	0.161	0.95 (0.80-1.12)	0.542	1.12 (0.95-1.32)	0.188
Multiple myeloma cancer	552	1.00 (ref.)	1.09 (0.84-1.40)	0.525	0.95 (0.73-1.22)	0.683	0.92 (0.71-1.19)	0.526
Leukaemia cancer	729	1.00 (ref.)	1.17 (0.93-1.47)	0.184	1.11 (0.88-1.39)	0.378	1.11 (0.88-1.40)	0.360
Overall cancer incidence	47684	1.00 (ref.)	0.95 (0.93-0.98)	<0.001	0.92 (0.90-0.95)	<0.001	0.93 (0.91-0.96)	<0.001
Cancer mortality	9888	1.00 (ref.)	0.83 (0.78-0.88)	<0.001	0.82 (0.77-0.87)	<0.001	0.81 (0.77-0.86)	<0.001

Cox proportional hazards regression models adjusted for age at recruitment, sex, ethnicity, education, TDI, BMI, smoking, diet, sleep duration, frequency of alcohol intake, physical activity, hypertension medication, cholesterol-lowering medications, insulin, creatinine, cystatin C, glucose, HbA1c, TG and overall health rating. Female corpus uteri and male prostate cancers were not adjusted for sex due to their sex-specificity.

Supplementary Figures

**Fig. S1** Cohort exclusions of the study participants

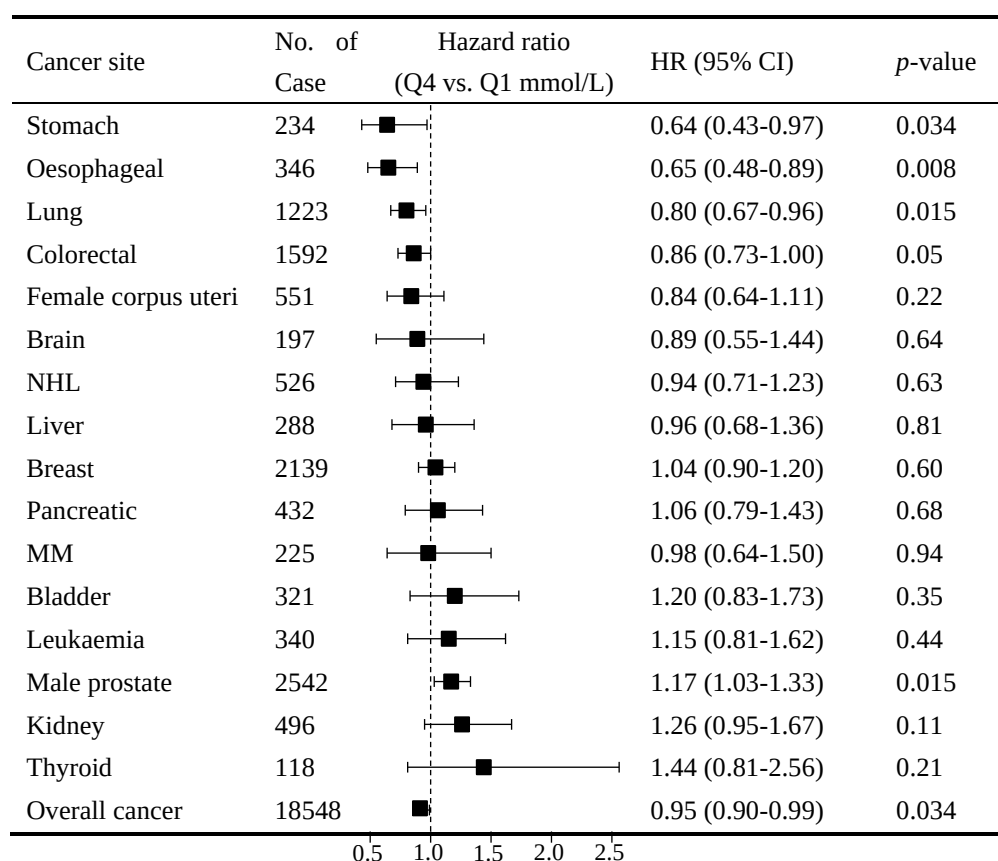


Fig. S2 HRs (95% CIs) for 16 site-specific cancers and overall cancer incidences according to serum urea categories when using a competing risk analysis

NHL, non-Hodgkin lymphoma. MM, Multiple myeloma. The competing risk models were adjusted for age at recruitment, sex, ethnicity, education, TDI, BMI, smoking, diet, sleep duration, frequency of alcohol intake, physical activity, hypertension medication, cholesterol-lowering medications, insulin, creatinine, cystatin C, glucose, HbA1c, TG and overall health rating. Female corpus uteri and male prostate cancers were not adjusted for sex due to their sex-specificity. The lowest quartile (Q1) of serum urea concentration was considered the reference group.

Supplementary Methods

Method S1. Assessment of covariates

Age at recruitment: age when attended assessment center (years).

Sex: female, male.

Ethnicity: white ethnicity, other.

Education:

The original options were: College or University degree; A levels/AS levels or equivalent; O levels/GCSEs or equivalent; CSEs or equivalent; NVQ or HND or HNC or equivalent; Other professional qualifications eg, nursing, teaching; None of the above; Prefer not to answer.

In this study, we divided the options into five categories: (1) Higher: college or university; (2) Middle: A levels/AS levels or equivalent, O levels/GCSEs or equivalent; (3) Lower: CSEs or equivalent, NVQ, HND, HNC, or equivalent; (4) Vocational: professional qualifications, e.g., nursing, teaching; (5) Other.

Townsend deprivation index (TDI):

The TDI was calculated immediately prior to the participant joining UK Biobank. Based on the preceding national census output areas. Each participant is assigned a score corresponding to the output area in which their postcode is located. The TDI combined information on non-homeownership, household overcrowding, non-car ownership, and unemployment at recruitment, with a lower score indicating a higher socioeconomic status.

Body mass index (BMI):

BMI value is constructed from height and weight measured during the initial assessment centre visit (Kg/m^2).

Smoking status: never, previous, current smoking.

Alcohol intake frequency:

The touchscreen question “About how often do you drink alcohol?”. The original options were: Daily or almost daily; Three or four times a week; Once or twice a week; One to three times a month; Special occasions only; Never; Prefer not to answer.

In the present study, it was divided into three groups: (1) Low: never, special occasions only; (2) Middle: one to three times a month; once or twice a week; (3) High: three or four times a week; daily or almost daily.

Physical activity frequency:

The touchscreen question “In a typical WEEK, on how many days did you do 10 minutes or more of moderate physical activities like carrying light loads, cycling at a normal pace? (Do not include walking)? ” and “In a typical WEEK, how many days did you do 10 minutes or more of vigorous physical activity? (These are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting)”. Units of measurement are days/week.

We add these two results and divide them by 2, and the final results are divided into three categories: (1) Low: ≤ 1 ; (2) Moderate: > 1 and ≤ 4 ; (3) High: > 4 and ≤ 7 .

Diet:

We defined the following 7 healthy eating behaviors: (1) Fruits ≥ 3 servings/day (Field ID: 1309, 1319); (2) Vegetables ≥ 3 servings/day (Field ID: 1289, 1299); (3) Fish $\geq$ twice a week (Field ID: 1329, 1339); (4) Whole grains ≥ 3 servings/day (Field ID: 1448, 1438); (5) Processed meat $\leq$ once a week (Field ID: 1349); (6) Red meat $\leq$ twice a week (Field ID: 1369, 1379, 1389); (7) Refined grains ≤ 1 serving/day (Field ID: 1458, 1468).

Participants had at least the above four healthy eating habits, which are defined as a healthy diet, and others are defined as an unhealthy diet.

Sleep duration:

The touchscreen question "About how many hours sleep do you get in every 24 hours? (please include naps)". The following checks were performed: If answer < 1 then rejected; If answer > 23 then rejected; If answer < 3 then participant asked to confirm; If answer > 12 then participant asked to confirm. Units of measurement are hours/day.

Medication history of anti-cholesterol drugs, antihypertensive drugs, insulin

The touchscreen question "Do you regularly take any of the following medications? (You can select more than one answer)". The original options were: Cholesterol lowering medication; Blood pressure medication; Insulin; Hormone replacement therapy; Oral contraceptive pill or minipill; None of the above; Do not know; Prefer not to answer.

Moreover, the touchscreen question "Do you regularly take any of the following medications? (you can select more than one answer)". The original options were: Cholesterol lowering medication; Blood pressure medication; Insulin; None of the above; Do not know; Prefer not to answer.

Medication history of anti-cholesterol drugs, anti-hypertensive drugs, or insulin selected for any of the options above was categorized as Cholesterol lowering medication (yes, no), Blood pressure medication (yes, no), and insulin (yes, no).

Biomarkers:

Creatinine (continuous in umol/L): Data-Field 30700

Cystatin C (continuous in mg/L): Data-Field 30720

Glucose (continuous in mmol/L): Data-Field 30740

Glycated haemoglobin (HbA1c, continuous in mmol/mol): Data-Field 30750

Triglycerides (TG, continuous in mmol/L): Data-Field 30870

Overall health rating:

The touchscreen question "In general how would you rate your overall health?". The original options were: Excellent, Good, Fair, Poor.

Method S2. Assessment of missing values

Variables	Missing value	
	Number of participants	Proportion (%)
Education	1648	1.5
Ethnicity	310	0.3
Body mass index	397	0.4
Moderate activity frequency	8055	7.4
Vigorous activity frequency	8383	7.7
Smoking status	639	0.6
Alcohol consumption frequency	226	0.2
Townsend deprivation index	149	0.1
Overall health rating	808	0.7
Sleep duration	1078	1.0
Creatinine	20	0.02

Cystatin C	91	0.1
Glucose	6726	6.2
Glycated haemoglobin	5488	5.1
Triglycerides	43	0.04

The options for blank, "don't know" and "don't want to answer" were defined as missing values.