Text S1 Definition of chronic disease.

According to the published description on NHANES database, chronic disease count was defined as the number of the following six conditions, including diabetes, coronary disease, hypertension, asthma, arthritis (rheumatoid arthritis, osteoarthritis), and 30 site-specific cancers.

Reference: Patel CJ, et al. A database of human exposomes and phenomes from the US National Health and Nutrition Examination Survey. Sci Data. 2016 Oct 25;3:160096.

Table S1 Environmental and clinical phenotypes included in the PheWAS.

Category	Number	Number of Validations
Body measurements	31	0
Blood routine	19	3
Biochemistry	76	7
Nutritional status	42	3
Urine test	78	1
Infection status	38	0
Disease history	39	3
Drugs used	204	0
Lifestyle	46	0
Living condition	14	0
Dietary	208	0
Drug addiction	14	0
Dioxins	29	0
Polychlorinated biphenyls	35	0
Pesticides	34	0
Phenols	9	0
Polybrominated diphenyl ethers	15	0
Polyfluorinated compounds	11	0
Volatile organic compounds	43	0

Table S2 Logistic regressions show associations between retinol with CKD in subgroup analysis.

Subgroup	Events/Participants	Odds Ratio (95%CI)	P value	P for interaction
Gender				0.190
Male	7571/15815	3.06 (2.70-3.48)	<0.001	
Female	8244/15815	2.74 (2.42-3.10)	<0.001	
Race				0.005
White	8089/15815	2.58 (2.31-2.90)	<0.001	
Black	3061/15815	3.79 (3.11-4.63)	<0.001	
Others	4665/15815	3.09 (2.52-3.80)		
Age, years				<0.001
Age≥46	8188/15815	2.60 (2.40-2.81)	<0.001	
Age < 46	7627/15815	10.2 (6.23-16.56)	<0.001	
BMI, kg/m^2				0.022
BMI≥30	5217/15815	3.33 (2.83-3.91)	<0.001	
BMI < 30	10598/15815	2.76 (2.48-3.07)	<0.001	
Diabetes				0.291
With diabetes	1791/15815	3.06 (2.58-3.63)	<0.001	
Free from diabetes	14024/15815	2.76 (2.48-3.06)	<0.001	
Hypertension				0.017
With hypertension	5041/15815	2.96 (2.64-3.31)	<0.001	
Free from hypertension	10774/15815	2.40 (2.06-2.79)	<0.001	

Table S3 Logistic regressions show associations between RDW with CKD in subgroup analysis.

Subgroup	Events/Participants	Odds Ratio (95%CI)	P value	P for interaction
Gender				0.015
Male	7571/15815	0.91 (0.85-0.97)	<0.001	
Female	8244/15815	0.91 (0.85-0.97)	<0.001	
Race				0.782
White	8089/15815	0.92 (0.86-0.98)	<0.001	
Black	3061/15815	0.88 (0.81-0.95)	<0.001	
Others	4665/15815			
Age, years				0.679
Age≥46	8188/15815	0.88 (0.82-0.93)	<0.001	
Age < 46	7627/15815	0.97 (0.89-1.05)	<0.001	
BMI, kg/m^2				0.194
BMI≥30	5217/15815	0.99 (0.91-1.08)	<0.001	
BMI < 30	10598/15815	0.91 (0.82-1.00)	<0.001	
Diabetes				0.396
With diabetes	1791/15815	0.89 (0.83-0.95)	<0.001	
Free from diabetes	14024/15815	0.94 (0.88-1.01)	<0.001	
Hypertension				0.013
With hypertension	5041/15815	0.91 (0.85-0.96)	<0.001	
Free from hypertension	10774/15815	0.92 (0.84-1.00)	<0.001	

Table S4 Logistic regressions show associations between C-peptide with CKD in subgroup analysis.

Subgroup	Events/Participants	Odds Ratio (95%CI)	P value	P for interaction
Gender				0.985
Male	7571/15815	0.91 (0.85-0.97)	<0.001	
Female	8244/15815	0.91 (0.85-0.97)	<0.001	
Race				0.278
White	8089/15815	0.92 (0.86-0.98)	<0.001	
Black	3061/15815	0.88 (0.81-0.95)	<0.001	
Others	4665/15815			
Age, years				0.023
Age≥46	8188/15815	0.88 (0.82-0.93)	<0.001	
Age < 46	7627/15815	0.97 (0.89-1.05)	<0.001	
BMI, kg/m^2				0.285
BMI≥30	5217/15815	0.99 (0.91-1.08)	<0.001	
BMI < 30	10598/15815	0.91 (0.82-1.00)	<0.001	
Diabetes				0.298
With diabetes	1791/15815	0.89 (0.83-0.95)	<0.001	
Free from diabetes	14024/15815	0.94 (0.88-1.01)	<0.001	
Hypertension				0.001
With hypertension	5041/15815	0.91 (0.85-0.96)	<0.001	
Free from hypertension	10774/15815	0.92 (0.84-1.00)	<0.001	

Figure S1 Heatmap showing Pearson coefficient correlations between validated phenotypes

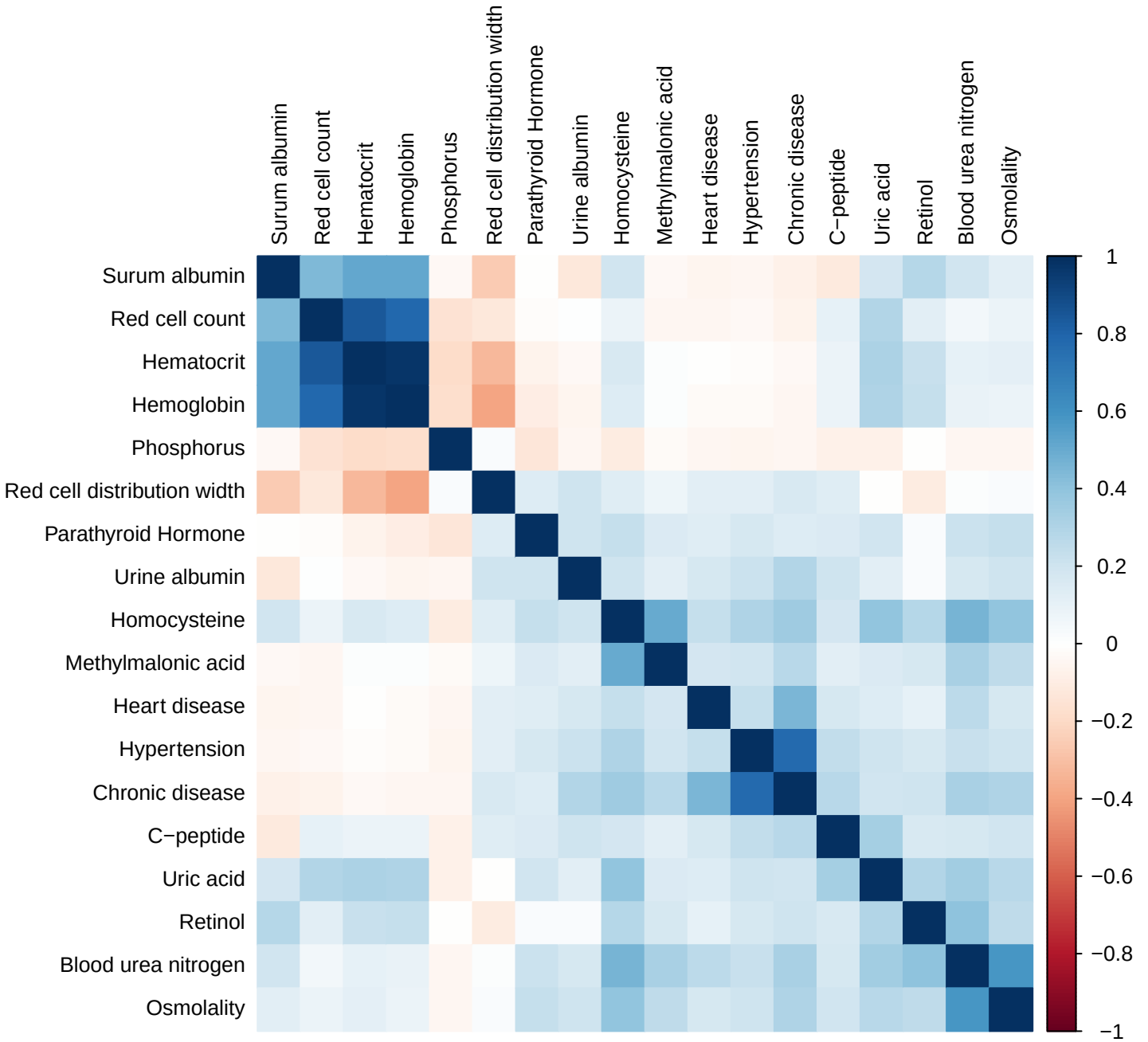
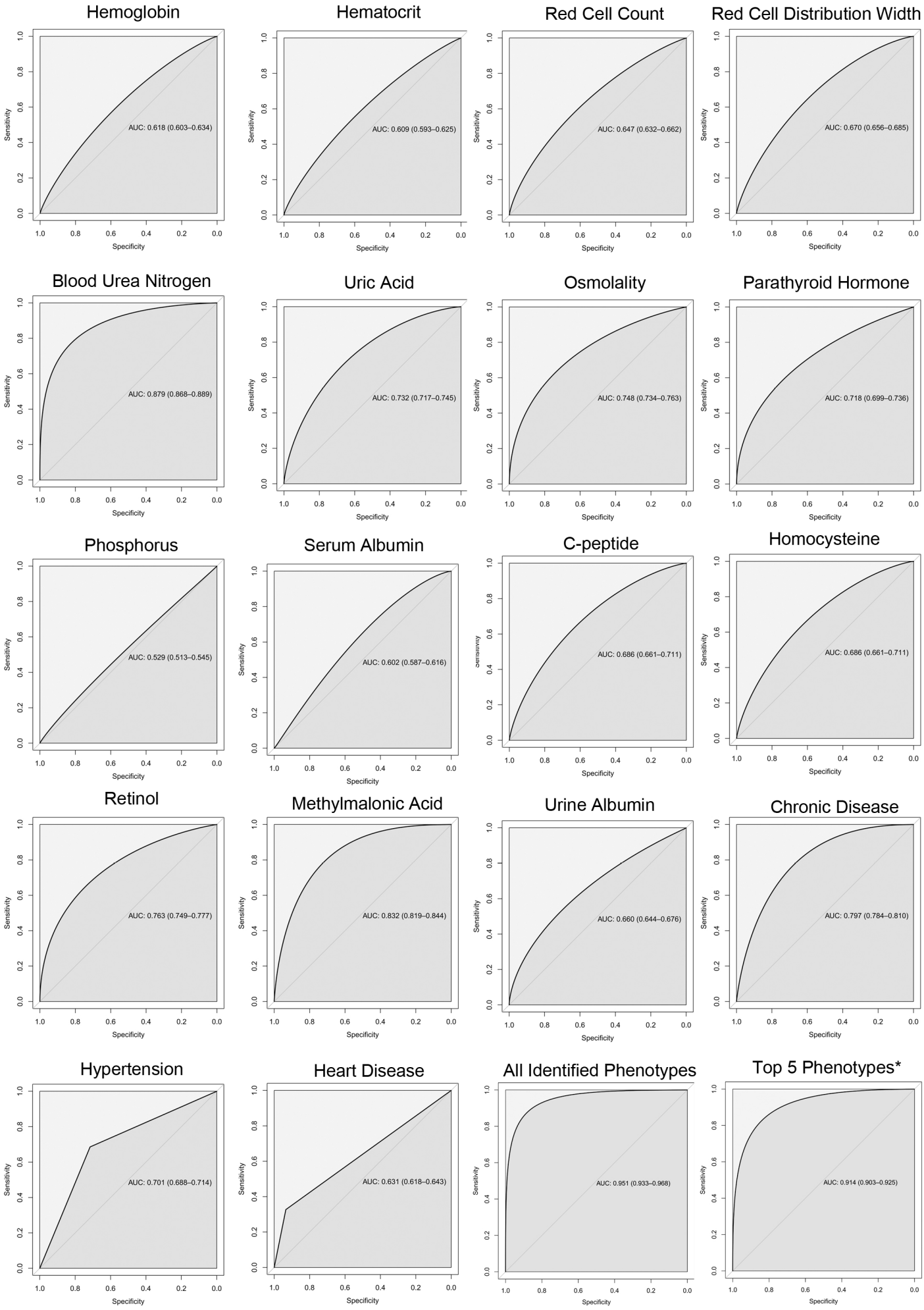
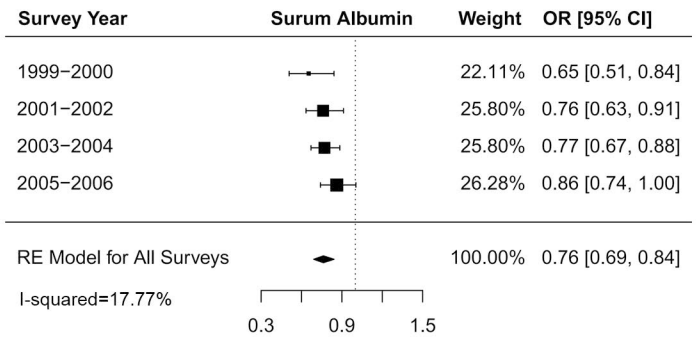


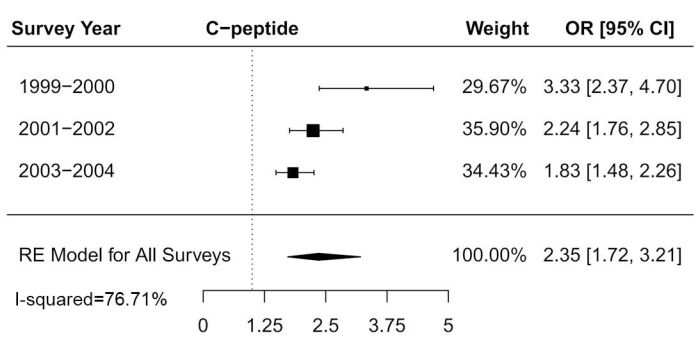
Figure S2 ROC curves of all identified phenotypes

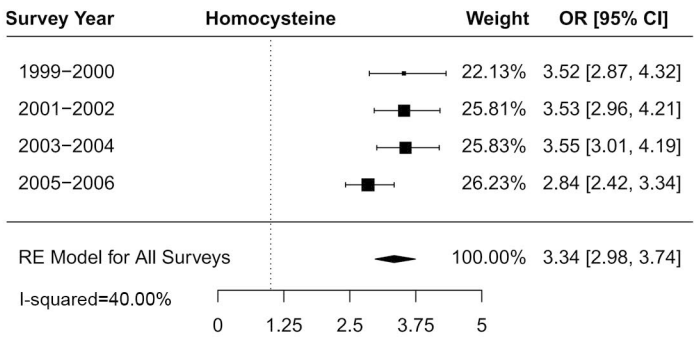


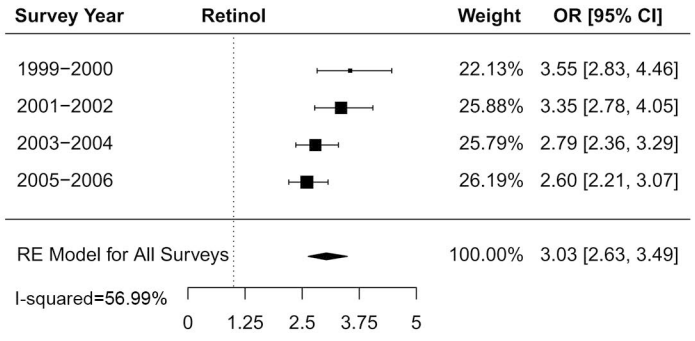
* Top 5 phenotypes: HCY, retinol, PTH, osmolality, serum albumin

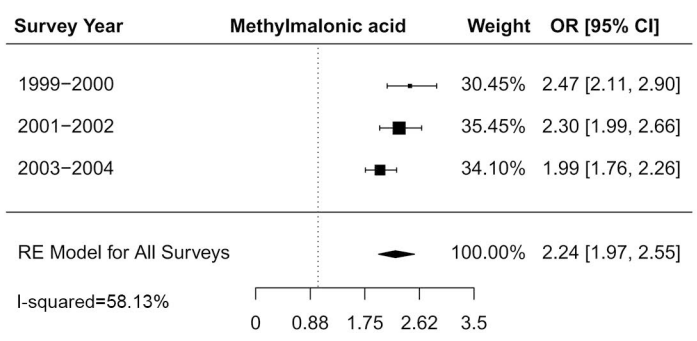
Figure S3 Random-effect META-analyses of all identified phenotypes per survey

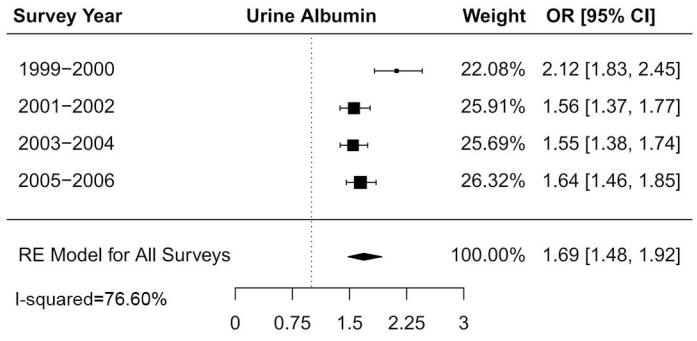


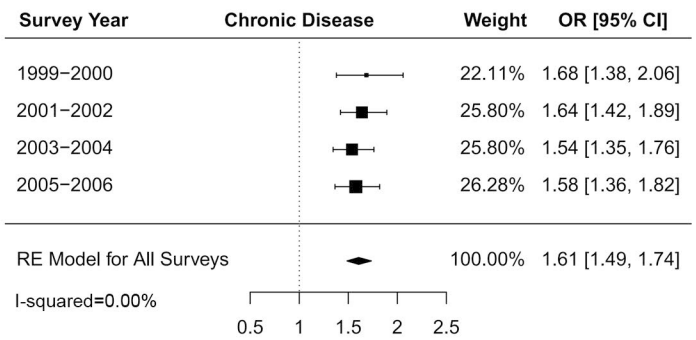


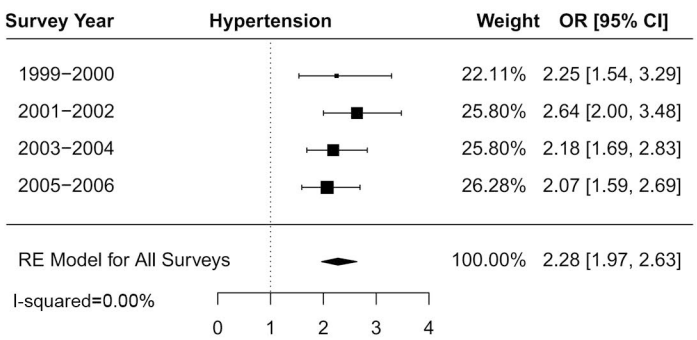


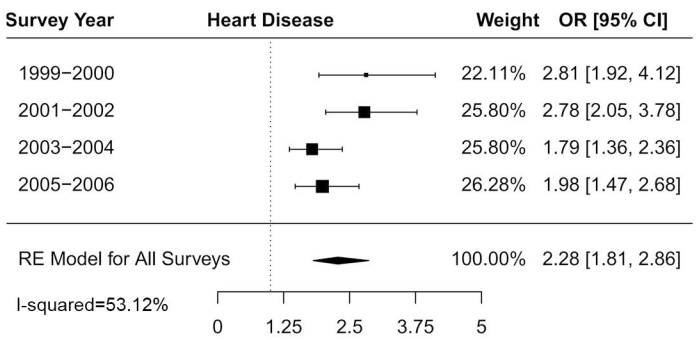


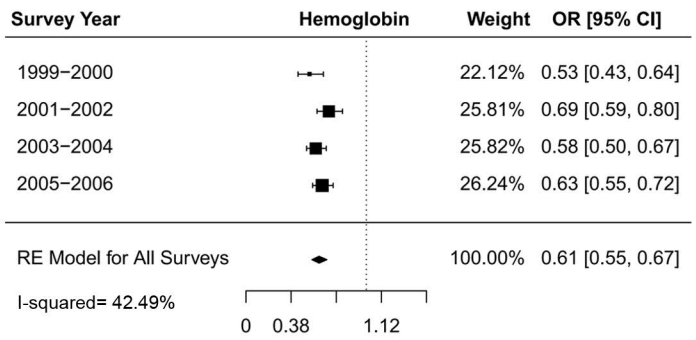


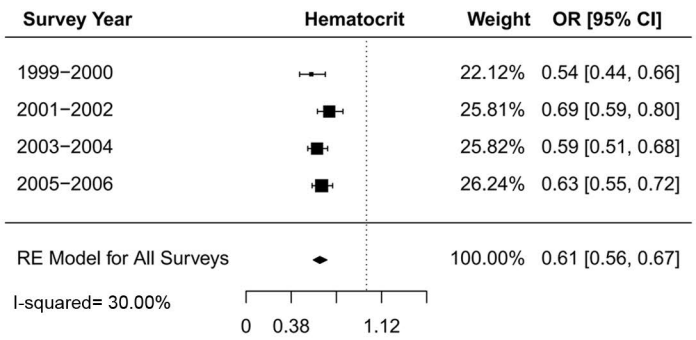


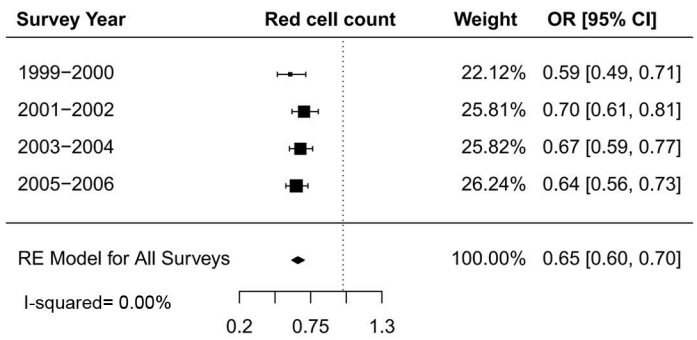


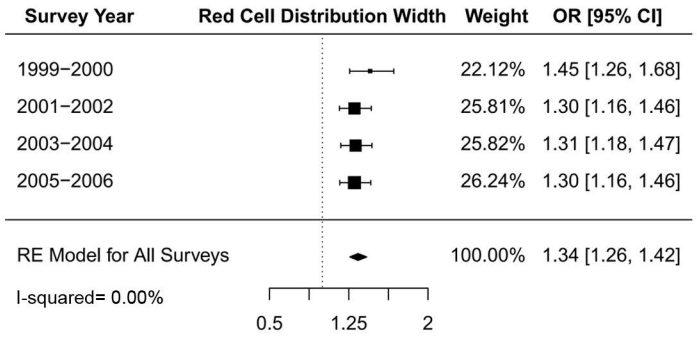


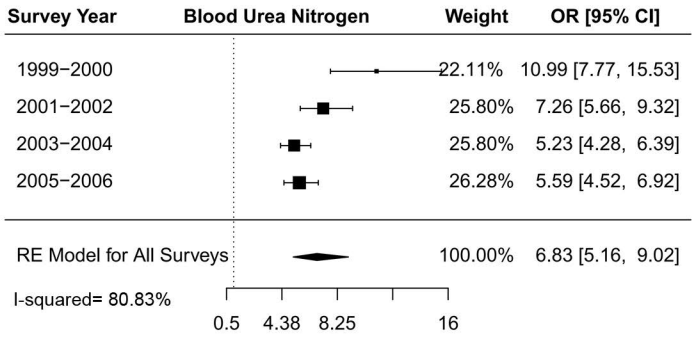


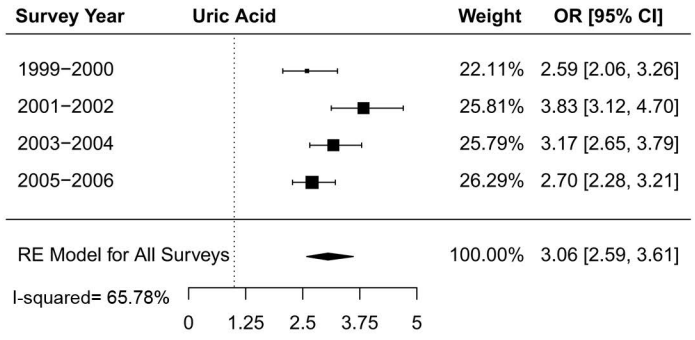

Survey Year
Hemoglobin
Weight
OR [95% CI]
1999−2000
22.12%
0.53 [0.43, 0.64]
2001−2002
25.81%
0.69 [0.59, 0.80]
2003−2004
25.82%
0.58 [0.50, 0.67]
2005−2006
26.24%
0.63 [0.55, 0.72]
RE Model for All Surveys
100.00%
0.61 [0.55, 0.67]
I-squared= 42.49%
0
0.38
1.12

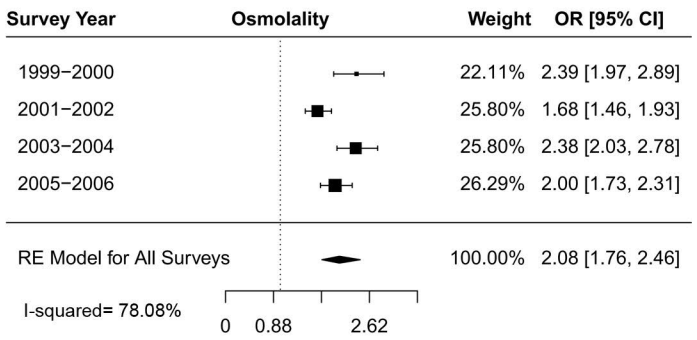

Survey Year
Hematocrit
Weight
OR [95% CI]
1999−2000
22.12%
0.54 [0.44, 0.66]
2001−2002
25.81%
0.69 [0.59, 0.80]
2003−2004
25.82%
0.59 [0.51, 0.68]
2005−2006
26.24%
0.63 [0.55, 0.72]
RE Model for All Surveys
100.00%
0.61 [0.56, 0.67]
I-squared= 30.00%
0
0.38
1.12

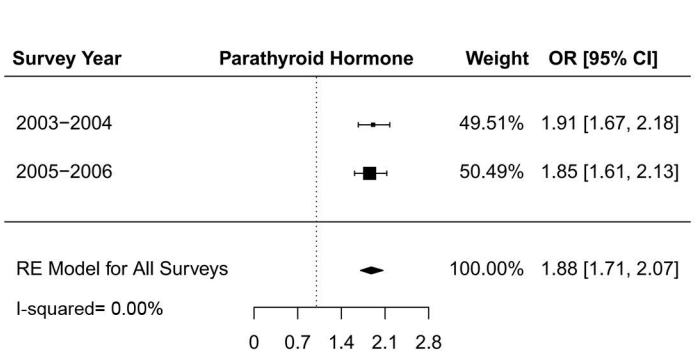

Survey Year
Red cell count
Weight
OR [95% CI]
1999−2000
22.12%
0.59 [0.49, 0.71]
2001−2002
25.81%
0.70 [0.61, 0.81]
2003−2004
25.82%
0.67 [0.59, 0.77]
2005−2006
26.24%
0.64 [0.56, 0.73]
RE Model for All Surveys
100.00%
0.65 [0.60, 0.70]
I-squared= 0.00%
0.2
0.75
1.3

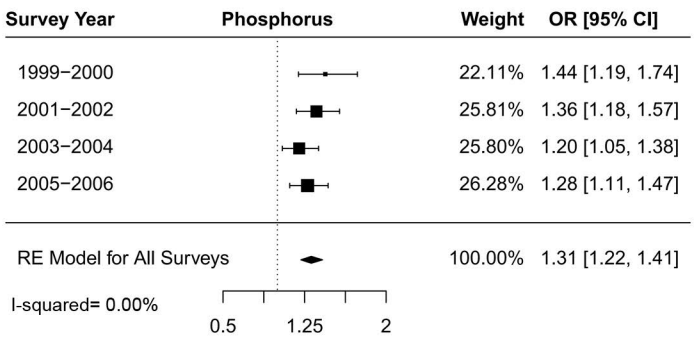

Survey Year
Red Cell Distribution Width
Weight
OR [95% CI]
1999−2000
22.12%
1.45 [1.26, 1.68]
2001−2002
25.81%
1.30 [1.16, 1.46]
2003−2004
25.82%
1.31 [1.18, 1.47]
2005−2006
26.24%
1.30 [1.16, 1.46]
RE Model for All Surveys
100.00%
1.34 [1.26, 1.42]
I-squared= 0.00%
0.5
1.25
2


Survey Year
Blood Urea Nitrogen
Weight
OR [95% CI]
1999−2000
22.11%
10.99 [7.77, 15.53]
2001−2002
25.80%
7.26 [5.66, 9.32]
2003−2004
25.80%
5.23 [4.28, 6.39]
2005−2006
26.28%
5.59 [4.52, 6.92]
RE Model for All Surveys
100.00%
6.83 [5.16, 9.02]
I-squared= 80.83%
0.5
4.38
8.25
16


Survey Year
Uric Acid
Weight
OR [95% CI]
1999−2000
22.11%
2.59 [2.06, 3.26]
2001−2002
25.81%
3.83 [3.12, 4.70]
2003−2004
25.79%
3.17 [2.65, 3.79]
2005−2006
26.29%
2.70 [2.28, 3.21]
RE Model for All Surveys
100.00%
3.06 [2.59, 3.61]
I-squared= 65.78%
0
1.25
2.5
3.75
5


Survey Year
Osmolality
Weight
OR [95% CI]
1999−2000
22.11%
2.39 [1.97, 2.89]
2001−2002
25.80%
1.68 [1.46, 1.93]
2003−2004
25.80%
2.38 [2.03, 2.78]
2005−2006
26.29%
2.00 [1.73, 2.31]
RE Model for All Surveys
100.00%
2.08 [1.76, 2.46]
I-squared= 78.08%
0
0.88
2.62


Survey Year
Parathyroid Hormone
Weight
OR [95% CI]
2003−2004
49.51%
1.91 [1.67, 2.18]
2005−2006
50.49%
1.85 [1.61, 2.13]
RE Model for All Surveys
100.00%
1.88 [1.71, 2.07]
I-squared= 0.00%
0
0.7
1.4
2.1
2.8


Survey Year
Phosphorus
Weight
OR [95% CI]
1999−2000
22.11%
1.44 [1.19, 1.74]
2001−2002
25.81%
1.36 [1.18, 1.57]
2003−2004
25.80%
1.20 [1.05, 1.38]
2005−2006
26.28%
1.28 [1.11, 1.47]
RE Model for All Surveys
100.00%
1.31 [1.22, 1.41]
I-squared= 0.00%
0.5
1.25
2