British Journal of Nutrition (2022), 127, 993–999 doi:10.1017/S0007114521001690

Kidney function decline is associated with an accelerated increase in plasma homocysteine in older adults: a longitudinal study

Hui Zhang[1†], Yi Li[1,2†], Meng Hao[1], Xiaoyan Jiang[3], Jiucun Wang[1], Li Jin[1,2], Zhijun Bao[4*] and Xiaofeng Wang[1,4,5*]

[1]*State Key Laboratory of Genetic Engineering, Collaborative Innovation Center for Genetics and Development, School of Life Sciences and Human Phenome Institute, Fudan University, Shanghai, People's Republic of China*
[2]*Institute for Six-sector Economy, Fudan University, Shanghai, People's Republic of China*
[3]*Key Laboratory of Arrhythmias of the Ministry of Education of China, Tongji University School of Medicine, Shanghai, People's Republic of China*
[4]*Shanghai Key Laboratory of Clinical Geriatric Medicine and Huadong Hospital Clinical Research Center for Geriatric Medicine, Shanghai, People's Republic of China*
[5]*National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, Shanghai, People's Republic of China*

(Submitted 25 January 2021 – Final revision received 23 April 2021 – Accepted 12 May 2021 – First published online 24 May 2021)

Abstract

Few studies have been conducted to investigate the association of kidney function decline with the trajectories of homocysteine (Hcy) over time, using repeated measurements. We aimed to investigate the association of kidney function with changes in plasma Hcy levels over time. Data were collected from the Rugao Longevity and Ageing Study. In detail, plasma Hcy and creatinine levels were measured in both waves (waves 2, 3 and 4) during the 3·5-year follow-up (*n* 1135). Wave 2 was regarded as the baseline survey. The estimated glomerular filtration rate (eGFR) was calculated based on creatinine. Subjects were categorised into four groups according to quartiles of eGFR at baseline. Linear mixed-effect models were used to investigate the association of eGFR with subsequent plasma Hcy levels. The mean eGFR at baseline was 90·84 (SD 11·42) ml/min per 1·73 m^2. The mean plasma Hcy level was 14·09 (SD 6·82) at baseline and increased to 16·28 (SD 8·27) and 17·36 (SD 10·39) μmol/l during follow-ups. In the crude model, the interaction between time and eGFR at baseline was significant ($\beta = -0{\cdot}02$, 95 % CI −0·02, −0·01, $P = 0{\cdot}002$). After adjusting for confounding factors, a significant relationship remained ($\beta = -0{\cdot}02$, 95 % CI −0·02, −0·01, $P = 0{\cdot}003$), suggesting that kidney function decline at baseline was associated with a faster increase in Hcy levels. Kidney function decline is associated with a more pronounced increase in plasma Hcy levels. Further studies with longer follow-up periods and larger sample sizes are needed to validate our findings.

Key words: **Kidney function decline: Homocysteine: Older adults: Linear mixed-effect models**

Homocysteine (Hcy) is a sulphur amino acid by-product of methionine metabolism[1]. The levels of Hcy are affected by genetic alterations of methionine metabolism enzymes and the concentrations of vitamin B_{12}, vitamin B_6 and folic acid[2]. Mendelian randomisation studies have reported that Hcy is a causal factor for many diseases, such as Alzheimer's disease[3], stroke[4,5] and schizophrenia[6,7]. Randomised clinical trials also reported the benefit of Hcy-lowering therapy on improving cognitive function in mild cognitive impairment[8], reducing the risk of stroke[9,10], delaying the progression of chronic kidney disease among patients with mild-to-moderate chronic kidney disease[11,12] and ameliorating psychiatric symptoms in schizophrenia[13,14]. Hence, the metabolism of Hcy would be of importance to prevent and treat many diseases.

Kidney function plays an important role in Hcy metabolism[15,16]. Observational studies found that plasma Hcy concentration was elevated in moderate renal insufficiency[17]. Renal transplant recipients had significantly decreased plasma Hcy levels after renal transplant compared with that before renal transplant[18]. Kidney donors with a significantly decreased estimated glomerular filtration rate (eGFR) had greater Hcy levels than controls[19,20]. Although previous studies have suggested the

Abbreviations: eGFR, estimated glomerular filtration rate; Hcy, homocysteine.

* **Corresponding author:** Xiaofeng Wang, email wangxiaofeng@fudan.edu.cn; Zhijun Bao, email 2845054591@qq.com

† These authors contributed equally to this work.

important role of kidney function in Hcy metabolism, overwhelming studies have paid attention to the link between plasma Hcy levels and kidney function using cross-sectional[21–23] and longitudinal settings[24–26]; there is still a lack of studies investigating the relationship between kidney function and trajectories of plasma Hcy levels over time.

Trajectory analysis is more sensitive when exploring the course change in outcomes over time and reliably estimating the slope, illustrating the natural history of exposure-induced outcomes. Therefore, we aimed to explore the association of kidney function at baseline with the trajectories of Hcy levels using repeated measurements in a longitudinal cohort among older adults.

Methods

Study population

The Rugao Longevity and Ageing Study is an observational, prospective and community-based cohort study[27]. Its first survey was conducted in November 2014 (wave 1). Then, the second survey was conducted in April 2016 (wave 2). The third and fourth surveys were conducted in November 2017 (wave 3) and December 2019 (wave 4), respectively. Because plasma Hcy was not measured in wave 1, we included subjects in waves 2, 3 and 4 in this study. A total of 1824 older adults were recruited in wave 2. During the 3·5-year follow-up (from wave 2 to wave 4), 689 subjects were excluded because of a lack of plasma Hcy or creatinine data. Finally, a total of 1135 subjects with complete information in both waves were included. Additionally, wave 2 was regarded as the baseline survey in our analyses. This study was approved by the Human Ethics Committee of the School of Life Sciences of Fudan University. Informed consent was obtained from each participant.

Measurements and outcomes

Plasma Hcy and creatinine levels were measured in both waves. A chemiluminescence immunoassay was used to measure plasma Hcy levels in the biochemistry laboratory of Rugao People's Hospital. Serum creatinine concentration was measured based on the enzymatic method with the Cica Creatinine reagent (KANTO Chemical) and a Hitachi 7600 analyser (Hitachi). The eGFR was calculated using equations conducted by the Chronic Kidney Disease Epidemiology Collaboration for creatinine[28]. $eGFR = 144 \times (\text{creatinine (mg/dl)}/0{\cdot}7)^{-0{\cdot}329} \times (0{\cdot}993)^{\text{Age}}$, if female and creatinine $\leq 0{\cdot}7$; $eGFR = 144 \times (\text{creatinine (mg/dl)}/0{\cdot}7)^{-1{\cdot}209} \times (0{\cdot}993)^{\text{Age}}$, if female and creatinine $> 0{\cdot}7$; $eGFR = 141 \times (\text{creatinine (mg/dl)}/0{\cdot}9)^{-0{\cdot}411} \times (0{\cdot}993)^{\text{Age}}$, if male and creatinine $\leq 0{\cdot}9$; or $eGFR = 141 \times (\text{creatinine (mg/dl)}/0{\cdot}9)^{-1{\cdot}209} \times (0{\cdot}993)^{\text{Age}}$, if male and creatinine $> 0{\cdot}9$.

Subjects were categorised according to plasma Hcy level and eGFR. For plasma Hcy, subjects were defined as the elevated Hcy group when their Hcy was greater than 15 μmol/l; conversely, subjects were defined as the normal Hcy group when their Hcy was less than or equal to 15 μmol/l[29]. For kidney function, subjects were categorised into four groups according to quartiles of eGFR.

Covariates

Demographic, clinical characteristics and lifestyles were collected from the Rugao Longevity and Ageing Study. Demographic data included age, sex, marital status and educational years. Clinical characteristics included CVD, diabetes mellitus, hypertension, chronic lung disease, cognitive function decline (assessed by the revised Hasegawa's dementia scale and subjects with cognitive scores less than 21·5 were defined as cognitive decline[30]), antihypertension drugs, antidiabetic drugs and vitamin B_{12} concentration (in wave 2). CVD included cerebral infarction, stroke, cerebral haemorrhage, CHD, myocardial infarction and heart failure. Chronic lung disease included pulmonary tuberculosis, chronic bronchitis, asthma or chronic obstructive pulmonary disease. Participants who self-reported a diagnosis of diabetes mellitus, used medication for diabetes mellitus or had a fasting glucose greater than 125 mg/dl were coded as having diabetes mellitus. Lifestyles included smoking, alcohol consumption, sleep quality (assessed by the Pittsburgh Sleep Quality Index[31]) and BMI. Vitamin B_{12} was categorised into three groups according to tertiles (lowest third: ≤460 pmol/l; middle third: >460, ≤676 pmol/l; and highest third: > 676 pmol/l).

Statistical analysis

In this study, we described the characteristics of the study population at baseline stratified by quartiles of kidney function. Continuous and categorical variables are presented as the mean with standard deviation and frequency (%), respectively. Then, for longitudinal analyses to assess the effect of eGFR at baseline on subsequent levels of plasma Hcy during follow-ups, we used linear mixed-effect models to analyse the association of eGFR at baseline with subsequent plasma Hcy levels over time. A *P*-value (two-tailed) less than 0·05 was considered statistically significant. All analyses were conducted in the following three models: model 1: unadjusted; model 2: adjusted for age, sex, smoking, alcohol consumption, education, marital status, CVD, diabetes, hypertension, chronic lung disease, cognitive function and sleep quality; and model 3: adjusted for model 2 + vitamin B_{12} and BMI. Additionally, we also explored the effect of plasma Hcy levels at baseline (normal *v.* elevated) on subsequent levels of eGFR using linear mixed-effect models. Furthermore, we conducted sensitivity analyses in participants without CVD or diabetes in three models to validate our findings. All analyses were conducted by SPSS 22.0 and R (Version 3.6.1: www.r-project.org/).

Results

Characteristics of study population

The included sample characteristics across the three waves are presented in Table 1. In this study, a total of 1135 subjects were included. The mean age was 76·52 (SD 3·87) years. The mean plasma Hcy level was 14·09 (SD 6·82) μmol/l at baseline and then increased to 16·28 (SD 8·27) and 17·36 (SD 10·39) μmol/l at the 1·5-

British Journal of Nutrition

Table 1. Sample characteristics across three waves (*n* 1135) (Numbers and percentages)

	Wave 2 (baseline)		Wave 3 (1·5-year later)		Wave 4 (3·5-year later)	
	n	%	*n*	%	*n*	%
Age, years						
Mean	76·52		78·04		80·22	
SD	3·87		3·89		3·94	
Male	521	45·90	521	45·90	521	45·90
Educational years						
0 year	585	51·54	585	51·54	585	51·54
1–6 years	492	43·35	492	43·35	492	43·35
≥ 7 years	58	5·10	58	5·10	58	5·10
Married*	783	68·99	732	64·49	673	59·30
PSQI						
Mean	5·26		5·07		5·09	
SD	3·11		2·87		2·96	
Smoking	307	27·05	222	19·56	267	23·52
Alcohol consumption	404	35·59	346	30·48	364	32·07
BMI, kg/m^2						
Mean	23·83		24·31		23·87	
SD	3·53		7·15		3·96	
CVD	184	16·21	154	13·57	115	10·13
Diabetes	237	20·88	177	15·59	148	13·04
Hypertension	832	73·30	985	86·78	795	70·04
Cognitive decline	505	44·49	630	55·51	652	57·44
Chronic lung disease	167	14·71	101	8·90	78	6·87
Vitamin B_{12}, pmol/l						
Low (≤460)	375	33·04				
Middle (>460, ≤676)	375	33·04				
Highest (>676)	385	33·92				
Homocysteine, μmol/l						
Mean	14·09		16·28		17·36	
SD	6·82		8·27		10·39	
Normal Hcy	821	72·33	616	54·27	560	49·34
Elevated Hcy	314	27·67	519	45·73	575	50·66
eGFR, ml/min per 1·73 m^2						
Mean	90·84		85·13		77·16	
SD	11·42		11·64		13·17	
Creatinine						
Mean	0·63		0·72		0·81	
SD	0·19		0·19		0·24	

eGFR, estimated glomerular filtration rate; PSQI, Pittsburgh Sleep Quality Index.
* Married and living together.

and 3·5-year follow-ups, respectively ($P < 0·001$). The number of subjects with elevated plasma Hcy levels was 314 (SD 27·67 %) at baseline and then increased to 519 (SD 45·73 %) and 575 (SD 50·66 %) at the 1·5- and 3·5-year follow-ups, respectively. The mean eGFR was 90·84 (SD 11·42) ml/min per 1·73 m^2 at wave 2 and then increased to 85·13 (SD 11·64) and 77·16 (SD 13·17) ml/min per 1·73 m^2 at subsequent follow-ups ($P < 0·001$). The detailed characteristics of the study population stratified by eGFR at baseline are presented in Table 2.

Associations of estimated glomerular filtration rate at baseline with plasma homocysteine levels during follow-ups

Associations between eGFR at baseline and subsequent plasma Hcy levels during follow-ups are shown in Table 3. In crude models, the interaction between time and eGFR at baseline was significant ($\beta = -0·02$, 95 % CI − 0·02, −0·01, $P = 0·002$). After considering covariates, the interaction remained ($\beta = -0·02$, 95 % CI − 0·02, −0·01, $P = 0·003$), suggesting that increased kidney function is associated with a more pronounced decrease in plasma Hcy levels during follow-ups.

Additionally, we analysed the impact of different quartiles of eGFR at baseline on subsequent plasma Hcy levels (Table 3). The interaction term between time and quartile 1 of eGFR at baseline was significant in both crude and adjusted models (for crude models: $\beta = 0·49$, 95 % CI 0·17, 0·81, $P = 0·003$; for adjusted models: $\beta = 0·49$, 95 % CI 0·16, 0·81, $P = 0·003$, respectively). These results indicated a significant difference in the slope for plasma Hcy levels over time between quartiles 1 and 4. The plasma Hcy levels increased approximately 0·49 points faster per year for subjects in quartile 1 than in quartile 4. The graphic analyses revealed that subjects in quartile 1 had a faster increased trajectory in plasma Hcy levels compared with those in quartile 4 (Fig. 1).

Similarly, the interaction between time and eGFR at baseline was significant ($\beta = -0·01$, 95 % CI − 0·02, −0·00, $P = 0·043$) in both the crude and adjusted models after excluding participants without CVD or diabetes (online Supplementary Table S1 and Fig. S1).

Discussion

Principal findings

To our knowledge, this is the first study to explore the association of kidney function with longitudinal changes in Hcy levels over time using repeated measurements during a 3·5-year follow-up and illustrated that kidney function decline was associated with a more pronounced increase in plasma Hcy levels. Additionally, we adjusted for many clinical and lifestyle factors (especially age, hypertension, vitamin B_{12} level and cognitive function), which provided robust evidence that kidney function played an important role in Hcy metabolism.

Compared with previous studies

Few studies have investigated the trajectories of plasma Hcy levels at different levels of kidney function, describing both changes between the two surveys and the slope of change over time using repeated measurements. The National Health and Nutrition Examination Survey indicated a close association of renal insufficiency with an increased risk of elevated circulating Hcy in the general population using cross-sectional settings[32]. Consistently, plasma Hcy levels were significantly higher in subjects who had decreased kidney function in our study (Table 2). However, the findings in National Health and Nutrition Examination Survey were based on cross-sectional settings, which just demonstrated a link relationship between eGFR and Hcy levels. Our analyses were conducted using repeated measurements during the 3·5-year follow-up and observed a steeper increase in plasma Hcy concentrations in subjects with kidney function decline. Trajectory analysis is more sensitive for exploring the course change in outcome over time and reliably estimating the slope, illustrating the natural history of kidney function decline-induced Hcy levels. Therefore, our study

British Journal of Nutrition

Table 2. Characteristics of study population stratified by quartiles of eGFR at baseline (Numbers and percentages)

Characteristics	Quartile 1 (*n* 284) (≤86·25)		Quartile 2 (*n* 286) (>86·25, ≤91·79)		Quartile 3 (*n* 279) (>91·79, ≤97·64)		Quartile 4 (*n* 286) (>97·64)		
	n	%	*n*	%	*n*	%	*n*	%	*P*
Age, years									
Mean	79·06		76·89		75·59		76·52		<0·001
SD	3·83		3·65		3·26		3·18		
Males	149	52·46	133	46·50	121	43·37	118	41·26	0·043
BMI, kg/m^2									
Mean	23·97		23·57		23·94		23·84		0·505
SD	3·37		3·38		3·66		3·52		
Educational years									0·090
0 year	146	51·41	150	52·45	141	50·54	148	51·75	
1–6 years	117	41·20	119	41·61	123	44·09	133	46·50	
≥ 7 years	21	7·39	17	5·94	15	5·38	5	1·75	
Married*	186	65·49	201	70·28	192	70·25	200	69·93	0·538
PSQI									
Mean	5·04		5·25		5·35		5·43		0·092
SD	2·99		3·21		3·12		3·13		
Smoking	84	28·58	91	25·45	71	25·45	61	21·33	0·025
Alcohol consumption	99	34·86	105	36·71	103	36·92	97	33·92	0·852
CVD	57	20·07	39	13·64	51	18·28	37	12·94	0·054
Diabetes mellitus	52	18·31	54	18·88	66	23·66	58	20·28	0·392
Hypertension	230	80·98	196	68·53	204	73·12	202	70·63	0·005
Cognitive decline	118	41·55	139	48·60	117	41·94	131	45·80	0·274
Chronic lung disease	40	14·08	37	12·94	40	14·34	50	17·48	0·460
Vitamin B_{12}, pmol/l									0·385
Low third (≤460)	110	38·73	86	30·07	87	21·18	92	32·17	
Middle third (>460, ≤676)	88	30·99	101	35·31	91	32·62	95	33·22	
Highest third (>676)	86	30·28	99	34·62	101	36·20	99	34·62	
Homocysteine, μmol/l									
Mean	16·86		14·26		13·15		12·10		<0·001
SD	6·08		7·06		8·07		4·74		
Creatinine, mg/dl									
Mean	0·84		0·66		0·57		0·46		<0·001
SD	0·18		0·09		0·09		0·09		
eGFR, ml/min/1·73 m^2									
Mean	76·68		89·20		94·53		102·97		<0·001
SD	11·19		1·58		1·73		5·08		

eGFR, estimated glomerular filtration rate; PSQI, Pittsburgh Sleep Quality Index.
* Married: Married and living together.

Table 3. Associations of kidney function at baseline with subsequent plasma Hcy in all participants (*β*-coefficients and 95 % confidence intervals)

	Model 1			Model 2			Model 3		
	β	95 % CI	*P*	*β*	95 % CI	*P*	*β*	95 % CI	*P*
Kidney function at wave 2									
eGFR, mL/min per 1·73 m^2	−0·19	−0·23, −0·15	<0·001	−0·15	−0·19, −0·10	<0·001	−0·15	−0·19, −0·11	<0·001
Time, year	2·28	1·40, 3·16	<0·001	2·28	1·40, 3·16	<0·001	2·28	1·40, 3·16	<0·001
eGFR × time	−0·02	−0·02, −0·01	0·002	−0·02	−0·02, −0·01	0·002	−0·02	−0·02, −0·01	0·002
Kidney function quartiles									
eGFR Q3 (>91·79, ≤97·64)*									
Q3	0·89	−0·17, 1·95	0·101	0·56	−0·49, 1·60	0·301	0·64	−0·38, 1·67	0·226
Time	0·76	0·59, 0·92	<0·001	0·76	0·59, 0·92	<0·001	0·76	0·59, 0·93	<0·001
Q3 × time	−0·03	−0·27, 0·20	0·780	−0·03	−0·27, 0·20	0·779	−0·04	−0·27, 0·20	0·772
eGFR Q2 (>86·25, ≤91·79)*									
Q2	2·33	1·11, 3·55	0·0002	1·69	0·44, 2·95	0·009	1·78	0·55, 3·02	0·005
Time	0·76	0·59, 0·92	<0·001	0·76	0·59, 0·92	<0·001	0·76	0·59, 0·93	<0·001
Q2 × time	0·16	−0·07, 0·40	0·181	0·16	−0·07, 0·40	0·181	0·16	−0·07, 0·40	0·185
eGFR Q1 (≤86·25)*									
Q1 (≤86·25)	4·94	3·58, 6·29	<0·001	2·95	1·41, 4·48	<0·001	3·02	1·50, 4·54	<0·001
Time	0·76	0·53, 0·98	<0·001	0·76	0·53, 0·98	<0·001	0·76	0·53, 0·99	<0·001
Q1 × time	0·49	0·17, 0·81	0·003	0·49	0·17, 0·81	0·003	0·49	0·16, 0·81	0·003

eGFR, estimated glomerular filtration rate; Hcy, homocysteine. Model 1: unadjusted; model 2: adjusted for age, sex, smoking, alcohol consumption, education, marital status, CVD, diabetes, hypertension, chronic lung disease, cognitive function and sleep quality; model 3: adjusted for model 2 + Vitamin B_{12} and BMI.
* Compared with kidney function Q4 (>97·64 ml/min/1·73 m^2).

British Journal of Nutrition

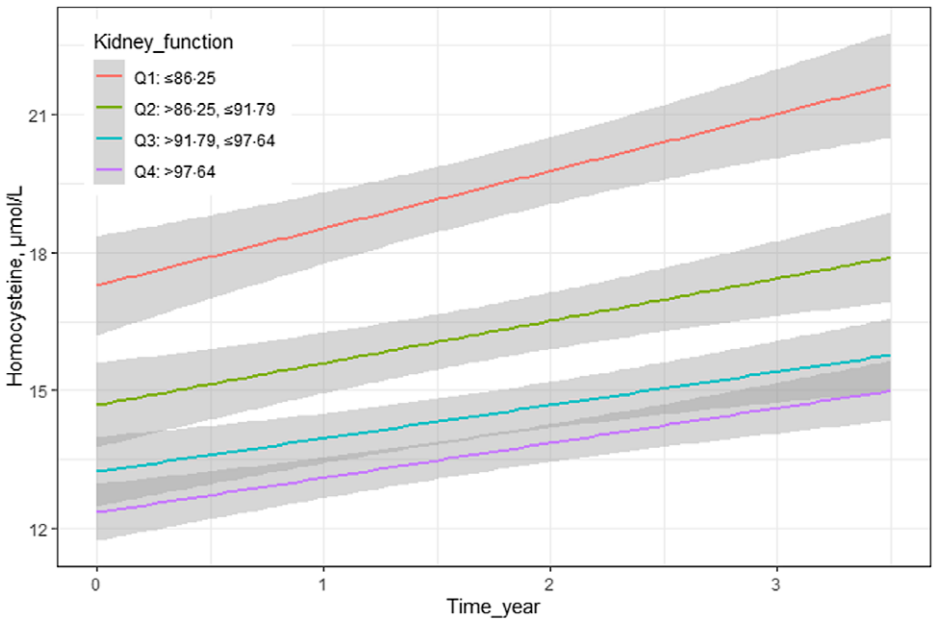

Figure 1 Longitudinal association of eGFR with subsequent plasma homocysteine during follow-ups.

provided more robust evidence to illustrate the significant association of kidney function with Hcy levels.

Coincidentally, renal transplant recipients had significantly decreased Hcy levels after renal transplant compared with before renal transplant[18]. It was likely that the increased Hcy levels in renal transplant recipients would be partially cleared after renal transplant with healthy kidneys, which was consistent with our findings that better kidney function has better efficiency for cleaning Hcy. In addition, kidney donors had acutely and persistently increased Hcy levels after renal transplantation at subsequent 6- and 36-month follow-ups[19,20,33]. It was conceivable that plasma Hcy levels may be increased considerably due to the cleaning efficiency of the kidney, because Hcy levels fell significantly after uninephrectomy. Unintendedly, the potential rejection of kidney allografts may affect efficient cleaning of Hcy. Since these studies were conducted in patients with severe renal disease or renal transplant, the generalisation of findings was limited to older populations. In our studies, we explored the association of kidney function with Hcy metabolism in a prospective and community-based cohort without severe renal disease or renal transplant, avoiding the potential effect of allograft rejection on Hcy levels. Hence, our studies would provide more generalised evidence than those studies conducted in patients with renal disease.

Possible mechanisms

The underlying cause of elevated Hcy levels in renal disease is not entirely understood, but it seems plausible that a reduction in renal Hcy clearance and metabolism was the cause[34]. Previous studies have reported that animal and human kidneys contain the necessary Hcy-metabolising enzymes, including trans-sulphuration and remethylation enzymes[34]. The normal kidney may compensate glomerular filtration by up- or down-regulating these pathways, thereby keeping Hcy levels constant[35]. However, the loss of metabolically active kidney tissue normally involved in Hcy handling would decrease Hcy clearance and increase plasma levels[34,35].

Strengths and limitations

Strengths were presented in our studies. Our study was conducted based on a community-based population in a prospective longitudinal cohort. It might be valuable to generalise the findings to the older population. The repeated measurement of plasma Hcy and creatinine levels was simultaneously measured from each subject at the same facility, which could ensure stability and reliability. The limitation of our study was the relatively small sample size, so it is necessary to recruit more individuals to verify our results in the future. In addition, the follow-up period was relatively short, which may limit the accuracy of the trajectories of plasma Hcy levels. Therefore, it is essential to conduct longer-term follow-ups with more points at different times to achieve more robust conclusions.

Conclusion

In summary, according to community-based and longitudinal settings, our study demonstrated that kidney function plays an important role in Hcy metabolism. Kidney function decline is associated with a more pronounced increase in plasma Hcy levels among older adults. Kidney function should be primarily and carefully considered when conducting Hcy-lowering therapy and regimens. Additionally, the study recommended that it was important and feasible to trigger Hcy-lowering interventions by improving kidney function. Further studies with longer follow-up periods and larger sample sizes are needed to validate our findings.

British Journal of Nutrition

Acknowledgements

The authors acknowledge all participants involved in the present study from the Rugao Longevity and Ageing Study. We acknowledge the support from the government of Rugao, the Public Health Bureau of Jiang'an Township and Rugao city, the Bureau of Civil Affairs, the Rugao People's Hospital and all the local village physicians.

This work was supported by grants from the National Key R&D Program of China (2018YFC2000400/2018YFC2000400-3), the National Natural Science Foundation of China (81571372) and the Postdoctoral Science Foundation of China (2018 M640333).

Z. H., L. Y. and W. X. designed the research; Z. H., L. Y., J. X. and W. J. conducted the research; Z. H., L. Y. and H. M. analysed the data and performed the statistical analyses. Z. H., L. Y. and W. X. wrote the paper; Z. H. and W. X. had primary responsibility for the final content; and all authors read and approved the final manuscript.

Dr. Xiaofeng Wang reports grants from the National Key R&D Program of China (2018YFC2000400) and the National Natural Science Foundation of China (81571372). Dr. Yi Li reports grants from the Postdoctoral Science Foundation of China (2018 M640333). The authors declare that they have no relevant financial interests.

Supplementary material

For supplementary materials referred to in this article, please visit https://doi.org/10.1017/S0007114521001690

References

1. Perna AF & Ingrosso D (2019) Homocysteine and chronic kidney disease: an ongoing narrative. *J Nephrol* **32**, 673–675.
2. Cianciolo G, De Pascalis A, Di Lullo L, *et al.* (2017) Folic acid and homocysteine in chronic kidney disease and cardiovascular disease progression: which comes first? *Cardiorenal Med* **7**, 255–266.
3. Hu Q, Teng W, Li J, *et al.* (2016) Homocysteine and Alzheimer's disease: evidence for a causal link from Mendelian randomization. *J Alzheimer's Dis: JAD* **52**, 747–756.
4. Casas JP, Bautista LE, Smeeth L, *et al.* (2005) Homocysteine and stroke: evidence on a causal link from Mendelian randomisation. *Lancet* **365**, 224–232.
5. Larsson SC, Traylor M & Markus HS (2019) Homocysteine and small vessel stroke: a Mendelian randomization analysis. *Ann Neurol* **85**, 495–501.
6. Numata S, Kinoshita M, Tajima A, *et al.* (2015) Evaluation of an association between plasma total homocysteine and schizophrenia by a Mendelian randomization analysis. *BMC Med Genet* **16**, 54.
7. Nishi A, Numata S, Tajima A, *et al.* (2014) Meta-analyses of blood homocysteine levels for gender and genetic association studies of the MTHFR C677T polymorphism in schizophrenia. *Schizophrenia Bull* **40**, 1154–1163.
8. Ma F, Li Q, Zhou X, *et al.* (2019) Effects of folic acid supplementation on cognitive function and Aβ-related biomarkers in mild cognitive impairment: a randomized controlled trial. *Eur J Nutr* **58**, 345–356.
9. Martí-Carvajal AJ, Solà I, Lathyris D, *et al.* (2017) Homocysteine-lowering interventions for preventing cardiovascular events. *Cochrane Database Syst Rev* **8**, CD006612.
10. Li Y, Huang T, Zheng Y, *et al.* (2016) Folic acid supplementation and the risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. *J Am Heart Assoc* **5**, e003768.
11. Xu X, Qin X, Li Y, *et al.* (2016) Efficacy of folic acid therapy on the progression of chronic kidney disease: the renal substudy of the china stroke primary prevention trial. *JAMA Intern Med* **176**, 1443–1450.
12. Li Y, Spence JD, Wang X, *et al.* (2020) Effect of vitamin B(12) levels on the association between folic acid treatment and CKD progression: a post hoc analysis of a folic acid interventional trial. *Am J Kidney Dis: Offic J Natl Kidney Found* **75**, 325–332.
13. Sakuma K, Matsunaga S, Nomura I, *et al.* (2018) Folic acid/methylfolate for the treatment of psychopathology in schizophrenia: a systematic review and meta-analysis. *Psychopharmacol* **235**, 2303–2314.
14. Firth J, Stubbs B, Sarris J, *et al.* (2017) The effects of vitamin and mineral supplementation on symptoms of schizophrenia: a systematic review and meta-analysis. *Psychol Med* **47**, 1515–1527.
15. Lewerin C, Ljungman S & Nilsson-Ehle H (2007) Glomerular filtration rate as measured by serum cystatin C is an important determinant of plasma homocysteine and serum methylmalonic acid in the elderly. *J Intern Med* **261**, 65–73.
16. Veldman BA, Vervoort G, Blom H, *et al.* (2005) Reduced plasma total homocysteine concentrations in Type 1 diabetes mellitus is determined by increased renal clearance. *Diabetic Med: J Br Diabetic Assoc* **22**, 301–305.
17. Samuelsson O, Lee DM, Attman PO, *et al.* (1999) The plasma levels of homocysteine are elevated in moderate renal insufficiency but do not predict the rate of progression. *Nephron* **82**, 306–311.
18. Arnadottir M, Hultberg B, Wahlberg J, *et al.* (1998) Serum total homocysteine concentration before and after renal transplantation. *Kidney Int* **54**, 1380–1384.
19. Kasiske BL, Anderson-Haag T, Ibrahim HN, *et al.* (2013) A prospective controlled study of kidney donors: baseline and 6-month follow-up. *Am J Kidney Dis: Offic J Natl Kidney Found* **62**, 577–586.
20. Kasiske BL, Anderson-Haag T, Israni AK, *et al.* (2015) A prospective controlled study of living kidney donors: three-year follow-up. *Am J Kidney Dis: Offic J Natl Kidney Found* **66**, 114–124.
21. Cohen E, Margalit I, Shochat T, *et al.* (2019) The relationship between the concentration of plasma homocysteine and chronic kidney disease: a cross sectional study of a large cohort. *J Nephrol* **32**, 783–789.
22. Chao MC, Hu SL, Hsu HS, *et al.* (2014) Serum homocysteine level is positively associated with chronic kidney disease in a Taiwan Chinese population. *J Nephrol* **27**, 299–305.
23. Shankar A, Wang JJ, Chua B, *et al.* (2008) Positive association between plasma homocysteine level and chronic kidney disease. *Kidney Blood Press Res* **31**, 55–62.
24. Xie D, Yuan Y, Guo J, *et al.* (2015) Hyperhomocysteinemia predicts renal function decline: a prospective study in hypertensive adults. *Sci Rep* **5**, 16268.
25. Ninomiya T, Kiyohara Y, Kubo M, *et al.* (2004) Hyperhomocysteinemia and the development of chronic kidney disease in a general population: the Hisayama study. *Am J Kidney Dis: Offic J Natl Kidney Found* **44**, 437–445.
26. Kong X, Ma X, Zhang C, *et al.* (2017) Hyperhomocysteinemia increases the risk of chronic kidney disease in a Chinese

middle-aged and elderly population-based cohort. *Int Urol Nephrol* **49**, 661–667.
27. Liu Z, Wang Y, Zhang Y, *et al.* (2015) Cohort profile: the Rugao Longevity and Ageing Study (RuLAS). *Int J Epidemiol* **45**, 1064–1073.
28. Levey AS, Stevens LA, Schmid CH, *et al.* (2009) A new equation to estimate glomerular filtration rate. *Ann Intern Med* **150**, 604–612.
29. Levi A, Cohen E, Levi M, *et al.* (2014) Elevated serum homocysteine is a predictor of accelerated decline in renal function and chronic kidney disease: a historical prospective study. *Eur J Intern Med* **25**, 951–955.
30. Imai YHK (1994) The Revised Hasegawa's Dementia Scale (HDS-R) – evaluation of its usefulness as a screening test for dementia. *J Hong Kong Coll Psychiatr* **4**, 20–24.
31. Buysse DJ, Reynolds CF, Monk TH, *et al.* (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatr Res* **28**, 193–213.
32. Francis ME, Eggers PW, Hostetter TH, *et al.* (2004) Association between serum homocysteine and markers of impaired kidney function in adults in the United States. *Kidney Int* **66**, 303–312.
33. Tsai MY, Aras O, Sozen H, *et al.* (2004) Plasma homocysteine levels in living kidney donors before and after uninephrectomy. *J Lab Clin Med* **143**, 340–343.
34. Garibotto G, Sofia A, Valli A, *et al.* (2006) Causes of hyperhomocysteinemia in patients with chronic kidney diseases. *Semin Nephrol* **26**, 3–7.
35. Wollesen F, Brattström L, Refsum H, *et al.* (1999) Plasma total homocysteine and cysteine in relation to glomerular filtration rate in diabetes mellitus. *Kidney Int* **55**, 1028–1035.