

RESEARCH ARTICLE

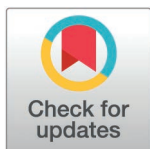
Association of intraindividual differences in estimated glomerular filtration rates based on cystatin C and creatinine with dementia: A cohort study of the UK Biobank

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Citation: Mao Z, Peng Y, Lin R, Guo X, Cui X, Yu Y, et al. (2026) Association of intraindividual differences in estimated glomerular filtration rates based on cystatin C and creatinine with dementia: A cohort study of the UK Biobank. PLoS One 21(3): e0344566. <https://doi.org/10.1371/journal.pone.0344566>

Editor: Donovan Anthony McGrowder, The University of the West Indies, JAMAICA

Received: November 9, 2025

Accepted: February 23, 2026

Published: March 6, 2026

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0344566>

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Abstract

Background

Dementia is a leading cause of cognitive decline, with Alzheimer's disease (AD) and vascular dementia (VaD) being the most common subtypes. The intraindividual difference between the estimated glomerular filtration rate based on cystatin C and creatinine (eGFR_{diff}) may serve as an indicator of the overall health status of an individual. However, the relationships between the eGFR_{diff} and dementia risk, dementia subtypes, dementia-related neuroimaging changes, and cognitive functions remain unclear.

Methods

This study analysed data from over 450,000 participants in the UK Biobank who were followed for up to 15 years. The estimated glomerular filtration rate based on cystatin C (eGFR_{cys}) and creatinine (eGFR_{cr}) was calculated using the CKD-EPI equation, and eGFR_{diff} was defined as the difference between these values (eGFR_{diff} = eGFR_{cys} - eGFR_{cr}). Multivariate Cox regression models were used to evaluate the associations between the eGFR_{diff} and all-cause dementia (ACD), AD, and VaD, whereas cross-sectional analysis were used to examine the relationship among the eGFR_{diff}, dementia-related neuroimaging changes, and cognitive functions.

Results

Over a median follow-up of 13.5 years, 8,710 participants developed dementia, including 3,910 with AD and 1,893 with VaD. Each one standard deviation increase in eGFR_{diff} was associated with a reduced risk of dementia, with hazard ratios (95%

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Data availability statement: Data cannot be shared publicly because individual-level data deposition is explicitly prohibited by the UK Biobank Material Transfer Agreement and Research Ethics Committee approval (16/NW/0274). Data are available from the UK Biobank Access Team (contact via access@ukbiobank.ac.uk or <https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access>) for researchers who meet the criteria for access to confidential data. The data underlying the results presented in the study are available from UK Biobank (Application ID: 98410).

Funding: This work was supported by the National Natural Science Foundation of China (grant No. 82273730 to YY), the Shanghai Municipal Natural Science Foundation (grant No. 22ZR1414900 to YY), and the Three-Year Public Health Action Plan of Shanghai (grants GWVI-11.2-XD10 and GWVI-11.1-01 to YY). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. There was no additional external funding received for this study.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: ACD: all-cause dementia, AD: Alzheimer's disease, VaD: vascular dementia, eGFR: estimated glomerular filtration rate, eGFR_{cr}: eGFR based on creatinine, eGFR_{cys}: eGFR based on cystatin C, WMHs: white matter hyperintensities, UKB: UK biobank, MRI: magnetic resonance imaging

confidence intervals) of 0.92 (0.90–0.94) for ACD, 0.94 (0.91–0.98) for AD, and 0.90 (0.85–0.94) for VaD. A negative eGFR_{diff} was associated with adverse neuroimaging changes, including lower total brain and gray matter volumes and higher white matter hyperintensities. Additionally, a negative eGFR_{diff} was associated with poorer performance across multiple cognitive domains.

Conclusion

A negative eGFR_{diff} was associated with an increased risk of dementia, adverse neuroimaging outcomes, and cognitive decline. These findings suggest that the eGFR_{diff} might be considered a potential associative indicator for dementia and cognitive impairment, suggesting potential clinical value in risk assessment and early intervention strategies.

Background

Dementia is a complex neurological disorder characterized by progressive and irreversible cognitive decline. In 2019, the incidence of dementia was reported to be 82.9 cases per 100,000 individuals in the UK (ranging from 70.6 to 95.1) and 95.0 cases per 100,000 individuals globally (ranging from 81.6 to 107.9) [1]. The prevalence of dementia is projected to increase from 50 million cases in 2020 to approximately 152 million cases by 2050 [2]. Alzheimer's disease (AD) and vascular dementia (VaD) are the primary subtypes of dementia, accounting for 60% and 20% of all cases, respectively [3]. Given the significant personal and socioeconomic burden of dementia, early detection and intervention are crucial for slowing disease progression and improving patients' quality of life [4,5]. Identifying reliable clinical markers in high-risk individuals is essential for facilitating timely diagnosis and management.

Although several studies have explored the relationships between the estimated glomerular filtration rate (eGFR) and dementia or cognitive impairment, the findings have been inconsistent [6–10]. These inconsistencies may be attributed to the differential influence of non-renal factors on eGFR estimation methods, particularly when using serum creatinine (eGFR_{cr}) versus cystatin C levels (eGFR_{cys}) [11,12]. Given the variability between these two measures, the difference between the eGFR_{cys} and eGFR_{cr} (eGFR_{diff}) has been proposed as a novel clinical marker for dementia or cognitive impairment. Recent studies suggest that the eGFR_{diff} is associated with various adverse clinical outcomes, including depression, heart failure, all-cause mortality, frailty, diabetic microvascular complications, cognitive decline, and motoric cognitive risk syndrome [13–21]. However, its relationship with specific dementia subtypes and subtle, preclinical dementia-related changes remains poorly understood. Understanding the potential role of the eGFR_{diff} as an indicator of early neurodegenerative processes could provide valuable insights into dementia risk and facilitate its early detection.

To address these knowledge gaps, this study investigated the associations between the eGFR_{diff} and the risk of developing all-cause dementia (ACD), AD, and

VaD in a large population-based cohort followed for up to 15 years. Given that the preclinical stage of dementia is characterized by subtle changes in brain structure and cerebrovascular pathology [22], this study hypothesized that $eGFR_{diff}$ serves as an early indicator of these dementia-related changes. To further explore this hypothesis, this study analysed associations between $eGFR_{diff}$, neuroimaging changes, and cognitive functions.

Materials and methods

Study design and population

This study utilized data from the UK Biobank (UKB), recruiting over 0.5 million participants aged 40–69 years from 22 centers across England, Scotland, and Wales between 2006 and 2010. At baseline, health-related data were collected through touchscreen questionnaires, verbal interviews, and physical measurements. Follow-up data were obtained through cohort-wide linkage to electronic health records. A total of 502,250 participants were initially enrolled. The exclusion criteria included withdrawal of consent, missing blood biochemistry data, self-reported or hospital-diagnosed cognitive impairment, dementia, or traumatic brain injury at baseline, and missing covariate data. The final study cohort included 458,668 participants (S1 Fig in [S1 File](#)). Neuroimaging and cognitive function analyses were performed in a subset of the baseline cohort who participated in the UKB imaging initiative [23]. During the imaging visits, brain magnetic resonance imaging (MRI) was performed using a 3 Tesla Siemens Skyra scanner equipped with software VD13 software and a standard 32-channel head coil. Imaging-derived phenotypes (IDPs) are generated via standardized image processing and quality control procedures [24]. Cognitive function was assessed via a touchscreen questionnaire [25]. After excluding participants with a history of cognitive impairment or dementia, 38,581 participants were included in the neuroimaging analyses, whereas 148,759 participants were included in the cognitive function analyses.

Ethical approval for the UKB study was granted by the North West Multi-Centre Research Ethics Committee (11/NW/0382). Informed consent was electronically obtained from all participants through a touchscreen. The current project was conducted under UK Biobank application ID: 98410. No additional ethical approval or patient re-contact was required.

Data collection

Assessment of eGFR differences. Serum creatinine and cystatin C levels were measured via enzymatic and latex-enhanced immunoturbidimetric assays, respectively. The $eGFR_{cys}$ and $eGFR_{cr}$ were calculated using the 2021 race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [11, 26]. The $eGFR_{diff}$ was defined as the $eGFR_{cys}$ minus the $eGFR_{cr}$, where negative values indicated a lower $eGFR_{cys}$ than the $eGFR_{cr}$, and positive values indicated a higher $eGFR_{cys}$ than the $eGFR_{cr}$. Additionally, the $eGFR_{ratio}$, defined as $eGFR_{cys}/eGFR_{cr}$, was calculated for sensitivity analysis. On a basis of predefined thresholds, $eGFR_{diff}$ was categorized into three groups: 1) negative $eGFR_{diff}$ (< -15 ml/min/1.73 m²); 2) midrange $eGFR_{diff}$ (-15 – 15 ml/min/1.73 m²); and 3) positive $eGFR_{diff}$ (≥ 15 ml/min/1.73 m²) [19,20,27]. The $eGFR_{ratio}$ was stratified into quartiles for sensitivity analysis.

Outcomes. The primary outcomes included incident ACD, AD, and VaD. Incident dementia was defined as the first hospital inpatient diagnosis of dementia or documentation of dementia as a contributing or underlying cause of death [28]. Both the inpatient datasets and death registers use the International Classification of Diseases (ICD) coding system. The UKB Outcome Adjudication Group compiled and validated ICD codes for dementia and its subtypes [29]. The dates of ACD, AD, and VaD diagnosis were considered the primary outcomes.

For neuroimaging analyses, IDPs were extracted from T1-weighted and T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) MRI images, which was [23]. MRI was acquired a median of 4.7 years (IQR 3.9–5.5) after baseline, ensuring that the exposure ($eGFR_{diff}$) temporally preceded the imaging outcomes. Imaging markers indicative of brain health included total brain volume, total white matter volume, total gray matter volume, bilateral hippocampus volume, and white matter hyperintensity (WMH) volume. WMH volume was log-transformed because of its skewed distribution.

Cognitive function including executive function, verbal and numerical reasoning, working memory, complex processing speed, verbal declarative memory, and non-verbal reasoning was assessed via validated touchscreen-based cognitive tests [25].

Covariates. Demographic, socioeconomic, clinical, and genetic factors including ethnic background, sex, were considered. 13 modifiable dementia risk factors identified by Livingston et al., which account for more than 40% of dementia onset were also considered to avoid potential confounders [4]. Sociodemographic, lifestyle, medical, and medication data were collected at baseline via touchscreen questionnaires. Anthropometric measurements such as height, weight, blood pressure, and cholesterol levels were obtained. Participants with cholesterol levels exceeding 5.7 mmol/L and low-density lipoprotein (LDL) levels above 2.6 mmol/L were classified as having high cholesterol or high LDL. Education was categorized as “college or above,” “high school or equivalent,” or “less than high school” [30]. Smoking status was classified as “never” or “ever,” and alcohol consumption was classified as “never,” “current,” or “current-excess” (more than 21 UK units) [4,31]. Physical activity was categorized by MET values, and socioeconomic status was estimated via the Townsend deprivation index [32,33]. Hearing and vision impairment were assessed by self-reported difficulties [34]. Diabetes, hypertension, depression, and obesity were identified through self-reports or relevant medications. To assess the effect of kidney function, $eGFR_{cr_cys}$, was included as a covariate [11,26]. Genetic risk factors were evaluated via APOE genotypes and a non-APOE polygenic risk score (PRS) specific to Alzheimer’s disease. The participants were categorized by APOE genotype and non-APOE PRS status. More details on the genetic methodology are available on the UK Biobank website(<https://biobank.ctsu.ox.ac.uk/showcase>).

Statistical analysis

Continuous variables are expressed as the means with standard deviations (SD) or medians with interquartile ranges (IQR) depending on their distribution. Comparisons between groups were performed using Student’s *t*-test or the Mann–Whitney U test, as appropriate, on the basis of data distribution. Categorical variables are expressed as counts (percentages) and analysed via the chi-square test or Fisher’s exact test, as appropriate. To examine the association between $eGFR_{diff}$ and incident dementia, Cox proportional hazard regression was performed, adjusting for potential confounders, including ethnicity, sex, Cho, LDL, education, smoking status, alcohol consumption, physical activity, TDI, social isolation, hearing impairment, vision impairment, diabetes, hypertension, depression, and obesity. The participants were followed-up from baseline assessments until dementia diagnosis, death, or censoring of hospital inpatient records (October 31, 2022, for England; August 31, 2022, for Scotland; and May 31, 2022, for Wales). The proportional hazard assumption was assessed using the Kaplan–Meier curves and Schoenfeld residual analysis. The results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Subgroup analyses were conducted to assess potential effect modification by APOE-genotype, non-APOE PRS, and physical impairment including hearing loss and vision loss. To investigate the associations between z scores of $eGFR_{diff}$ and neuroimaging outcomes as well as cognitive functions, multivariable linear regression analyses were performed, with adjustments made for the same covariates as in the Cox regression. The sensitivity analyses including the following: 1) multiple imputation with the default setting for missing covariate data [35], 2) exclusion of participants with an $eGFR_{cr}$ or $eGFR_{cys}$ less than 60 mL/min/1.73 m² due to the potential unreliability of their $eGFR$ measurements [36], 3) testing other $eGFR$ difference indices in place of the $eGFR_{diff}$ to ensure the reliability of the findings, 4) repeating the primary analyses within subgroups of participants with major pre-existing diseases, including diabetes, hypertension, and depression, and 5) lag-time analysis excluding participants diagnosed with dementia within 5 years post-exposure, assuming they may have had prevalent disease at baseline [37]. The reporting of our study adheres to the STROBE guidelines [38]. In addition, exploratory risk stratification and discrimination analyses were performed(details in S1 method in [S1 File](#)). All the statistical analyses were performed via R 4.0.3 software. A two-tailed *p*-value <0.05 was considered statistically significant.

Results

Baseline characteristics

The final study cohort comprised 458,668 participants with a mean age of 56.5 years (SD = 8.09), of whom 54.3% were female. [Table 1](#) summarizes the demographic and clinical characteristics of the study population. The participants with lower $eGFR_{diff}$ values were generally older and predominantly male. Health and social determinants also varied significantly across the $eGFR_{diff}$ groups. The negative $eGFR_{diff}$ group presented the highest levels of educational attainment, smoking and alcohol consumption rates, and TDI scores, with these levels progressively decreasing as $eGFR_{diff}$ increased. Additionally, this group demonstrated lower high-intensity but higher moderate-intensity physical activity, along with a higher prevalence of depression, obesity, and hypertension. The positive $eGFR_{diff}$ group presented the highest incidence of diabetes. LDL cholesterol levels were elevated in the midrange $eGFR_{diff}$ group, whereas vision impairment was most severe in the negative $eGFR_{diff}$ group ($p < 0.001$).

At baseline, the mean $eGFR_{cr}$ and $eGFR_{cys}$ values significantly differed across the $eGFR_{diff}$ groups. The mean $eGFR_{cr}$ values decreased with increasing $eGFR_{diff}$, whereas the mean $eGFR_{cys}$ values increased (both $p < 0.001$). A significant positive correlation was found between the $eGFR_{cys}$ and $eGFR_{cr}$ ($R = 0.604$, $p < 0.001$). The distributions of these measures are shown in S2 Fig in [S1 File](#).

Association of the $eGFR_{diff}$ with dementia

Over a median follow-up period of 13.5 years (interquartile range: 13.1–14.5 years), a total of 8,710 participants developed ACD, including 3,910 patients with AD, 1,893 patients with VaD, and 274 patients with frontotemporal dementia. Further analyses were not performed for frontotemporal dementia due to the low incidence rates. Kaplan–Meier survival curves and Schoenfeld residual analysis confirmed the proportional hazard assumption and revealed significant differences in outcome risks across the $eGFR_{diff}$ groups (S3 Fig in [S1 File](#)). Participants in the positive $eGFR_{diff}$ groups presented lower risks of developing ACD, AD, and VaD than the negative $eGFR_{diff}$ group ([Table 2](#)).

Specifically, for the incidence of ACD, the multivariable-adjusted HR was 0.88 (95% CI: 0.84–0.92) for the midrange $eGFR_{diff}$ group and 0.74 (95% CI: 0.65–0.86) for the positive $eGFR_{diff}$ group, compared with the negative $eGFR_{diff}$ group. A similar protective trend was observed for the incidence of AD, with adjusted HRs of 0.92 (95% CI: 0.85–0.98) in the midrange $eGFR_{diff}$ group and 0.80 (95% CI: 0.65–0.98) in the positive $eGFR_{diff}$ group. For the incidence of VaD, the adjusted HRs were 0.85 (95% CI: 0.77–0.94) for the midrange $eGFR_{diff}$ group and 0.67 (95% CI: 0.49–0.93) for the positive $eGFR_{diff}$ group. The dose–response relationships between the $eGFR_{diff}$ and the incidence of both ACD and AD primarily exhibited an L-shaped pattern, although nonlinearity tests revealed significant only in the incidence of ACD ([Fig 1](#)). For each 1 SD increase in $eGFR_{diff}$, the corresponding HRs (95% CIs) were 0.92 (range: 0.90–0.94) for the incidence of ACD, 0.94 (range: 0.91–0.98) for the incidence of AD, and 0.90 (range: 0.85–0.94) for the incidence of VaD ([Table 2](#)).

Subgroup analysis and sensitivity analysis

Stratified analyses based on APOE genotype, PRS, sex and ethnicity ([Fig 2](#)) revealed that the associations between the $eGFR_{diff}$ and incident dementia remained consistent across subgroups. However, the interactions observed between APOE genotype and ethnicity significantly modified the relationships between the $eGFR_{diff}$ and the incidence of ACD, while ethnicity alone significantly influenced the association between the $eGFR_{diff}$ and the incidence of VaD.

Sensitivity analyses demonstrated that the magnitude of associations remained stable after multiple imputations were applied for missing data (S1 Table in [S1 File](#)), excluding of participants with $eGFR_{cr}$ or $eGFR_{cys}$ values less than 60 mL/min/1.73 m² (S2 Table in [S1 File](#)), and when alternative $eGFR$ difference indices were used in place of $eGFR_{diff}$ (S3 Table, S4 Fig in [S1 File](#)). Notably, the associations between the $eGFR_{cr}$ or $eGFR_{cys}$ and the incidence of dementia varied before and after adjustment for kidney function, whereas the associations between the alternative $eGFR$ difference indices and

Table 1. Baseline Characteristics of Participants.

Variable ^a	Baseline eGFRdiff (mL/min/1.73 m ²)			Overall	P-value
	<-15 (N = 114925)	-15–15 (N = 320404)	≥15 (N = 23339)		
Mean Age (SD), years	58.4 (7.59)	56.1 (8.12)	53.1 (8.00)	56.5 (8.09)	<0.001
Ethnicity (White, %)	108788 (94.7%)	304591 (95.1%)	20749 (88.9%)	434128 (94.6%)	<0.001
Sex (Female, %)	58907 (51.3%)	176673 (55.1%)	13662 (58.5%)	249242 (54.3%)	<0.001
Education					
college or above	28910 (25.2%)	50116 (15.6%)	2520 (10.8%)	81546 (17.8%)	<0.001
high school or equivalent	56026 (48.8%)	159409 (49.8%)	12079 (51.8%)	227514 (49.6%)	
less than high school	29989 (26.1%)	110879 (34.6%)	8740 (37.4%)	149608 (32.6%)	
Non-smokers (%)	64238 (55.9%)	145937 (45.5%)	9330 (40.0%)	219505 (47.9%)	<0.001
Alcohol consumption (%)					
Never	7091 (6.2%)	11816 (3.7%)	746 (3.2%)	19653 (4.3%)	<0.001
Previous	6200 (5.4%)	9532 (3.0%)	528 (2.3%)	16260 (3.5%)	
Current	97276 (84.6%)	280907 (87.7%)	20602 (88.3%)	398785 (86.9%)	
Current, excessive	4358 (3.8%)	18149 (5.7%)	1463 (6.3%)	23970 (5.2%)	
Physical activity (MET-min/week)					
High	36948 (32.1%)	107119 (33.4%)	8043 (34.5%)	152110 (33.2%)	<0.001
Moderate	55311 (48.1%)	163290 (51.0%)	12024 (51.5%)	230625 (50.3%)	
Low	22666 (19.7%)	49995 (15.6%)	3272 (14.0%)	75933 (16.6%)	
Social isolate (%)	24772 (21.6%)	69766 (21.8%)	5516 (23.6%)	100054 (21.8%)	0.123
Median TDI (IQR)	-1.69 (-3.40 to 1.30)	-2.31 (-3.73 to 0.160)	-2.26 (-3.70 to 0.300)	-2.17 (-3.66 to 0.470)	<0.001
Cho (>5.7mmol/L)	55724 (48.5%)	155709 (48.6%)	10153 (43.5%)	221586 (48.3%)	0.523
LDL-C (>2.6mmol/L)	98793 (86.0%)	278597 (87.0%)	19932 (85.4%)	397322 (86.6%)	<0.001
Hearing loss (%)	13315 (11.6%)	37420 (11.7%)	2348 (10.1%)	53083 (11.6%)	0.401
Vision Impairment (%)	22260 (19.4%)	46998 (14.7%)	2473 (10.6%)	71731 (15.6%)	<0.001
NCDs					
Depression (%)	27897 (24.3%)	69818 (21.8%)	5115 (21.9%)	102830 (22.4%)	<0.001
Obesity (%)	43984 (38.3%)	63838 (19.9%)	3335 (14.3%)	111157 (24.2%)	<0.001
Diabetes (%)	105815 (92.1%)	306477 (95.7%)	22694 (97.2%)	434986 (94.8%)	<0.001
Hypertension (%)	80417 (70.0%)	184073 (57.5%)	11193 (48.0%)	275683 (60.1%)	<0.001
Mean eGFRcr_cys (SD), mL/min/1.73 m²	84.9 (14.5)	96.9 (18.3)	97.8 (17.2)	94.0 (18.1)	<0.001
Mean eGFRcr (SD), mL/min/1.73 m²	97.2 (10.3)	94.8 (13.5)	79.8 (11.7)	94.6 (13.1)	<0.001
Mean eGFRcys (SD), mL/min/1.73 m²	73.9 (11.6)	92.5 (14.5)	102 (11.0)	88.3 (16.2)	<0.001
Mean eGFRdiff (SD), mL/min/1.73 m²	-23.3 (6.92)	-2.33 (7.40)	22.3 (6.94)	-6.32 (13.3)	<0.001
Mean eGFRratio (SD)	0.759 (0.0727)	0.976 (0.0835)	1.29 (0.132)	0.938 (0.150)	<0.001

eGFRcr_cys, estimated glomerular filtration rate calculated using both creatinine and cystatin C; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; eGFRdiff, the difference between eGFRcys and eGFRcr; eGFRratio: the ratio between eGFRcys and eGFRcr; eGFRrd: the relative difference between eGFRcys and eGFRcr; TDI, Townsend deprivation index; MET, metabolic equivalent; LDL-C, serum low-density lipoprotein cholesterol; Cho: serum cholesterol; NCDs: Noncommunicable diseases.

^aThe values for categorical variables are given as numbers (%); values for continuous variables are given as median [Inter Quartile Range, IQR] or mean (standard deviation, SD).

<https://doi.org/10.1371/journal.pone.0344566.t001>

Table 2. Associations between difference in cystatin C- and creatinine-based estimated glomerular filtration rate and incident dementia.

Outcome and exposure	Cases (Rate per 100 person years)	Crude hazard ratio (95%CI)	Adjusted hazard ratio ^a (95%CI)
All cause dementia			
Categorical eGFR _{diff}			
Negative (~–15 ml/min/1.73 m ²)	3087 (2.04)	1.0 (ref)	1.0 (ref)
Midrange(~ 15 ml/min/1.73 m ²)	5404 (1.24)	0.60 (0.58 to 0.63)	0.88 (0.84 to 0.92)
Positive (> 15 ml/min/1.73 m ²)	219 (0.69)	0.33 (0.29 to 0.38)	0.74 (0.65 to 0.86)
Continuous eGFR _{diff} (per SD ml/min/1.73m ²)		0.73 (0.72 to 0.75)	0.92 (0.90 to 0.94)
Alzheimers disease			
Categorical eGFR _{diff}			
Negative (~–15 ml/min/1.73 m ²)	1309 (0.86)	1.0 (ref)	1.0 (ref)
Midrange(~ 15 ml/min/1.73 m ²)	2498 (0.57)	0.66 (0.61 to 0.70)	0.92 (0.85 to 0.98)
Positive (> 15 ml/min/1.73 m ²)	103 (0.32)	0.37 (0.30 to 0.45)	0.80 (0.65 to 0.98)
Continuous eGFR _{diff} (per SD ml/min/1.73m ²)		0.76 (0.74 to 0.79)	0.94 (0.91 to 0.98)
Vascular dementia			
Categorical eGFR _{diff}			
Negative (~–15 ml/min/1.73 m ²)	733 (0.48)	1.0 (ref)	1.0 (ref)
Midrange(~ 15 ml/min/1.73 m ²)	1121 (0.26)	0.53 (0.48 to 0.58)	0.85 (0.77 to 0.94)
Positive (> 15 ml/min/1.73 m ²)	39 (0.12)	0.25 (0.18 to 0.34)	0.67 (0.49 to 0.93)
Continuous eGFR _{diff} (per SD ml/min/1.73m ²)		0.67 (0.64 to 0.71)	0.90 (0.86 to 0.95)

HR, hazard ratio; CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia; eGFR_{cys}, estimated glomerular filtration rate calculated using both creatinine and cystatin C; eGFR_{diff}, the difference between creatinine-based estimated glomerular filtration rate; TDI, Townsend deprivation index; MET, metabolic equivalent; LDL-C, serum low-density lipoprotein cholesterol; Cho: serum cholesterol; NCDs: Noncommunicable

^a Age-scaled models were adjusted for eGFR_{cys}, Cho, LDL, education, smoking, drinking, physical activities, Townsend deprivation index (TDI), social isolate, hearing, eyesight, diabetes, hypertension, depression, and obesity. diseases.

<https://doi.org/10.1371/journal.pone.0344566.t002>

dementia incidence remained consistent (S5 Fig, S4-S6 Tables in [S1 File](#)). Additionally, a negative-control analysis using injury/poisoning codes (S7 Table in [S1 File](#)) showed no association with eGFR_{diff}, further supporting the specificity of our findings.

Optimal cut-off determination and risk Stratification of eGFR_{diff}

Using maximally selected rank statistics, the optimal cut-off value of the eGFR_{diff}-based score was identified as –8.813. Participants with eGFR_{diff} values ≤ –8.813 were classified as high risk, whereas those with values > –8.813 were classified as low risk. Kaplan–Meier curves demonstrated a significantly higher cumulative incidence of all-cause dementia in the high-risk group compared with the low-risk group (log-rank $p < 0.001$) (S6 Fig in [S1 File](#)).

Time-dependent ROC analyses showed good and increasing discrimination over follow-up for both models (S7 Fig in [S1 File](#)). At 5 years, the AUC was 0.801 for the UKBDRS model alone (Model 1) and increased to 0.810 after adding eGFR_{diff} (Model 2). At 10 years, the AUC increased from 0.821 in Model 1 to 0.825 in Model 2. At 15 years, the AUC further increased from 0.848 in Model 1 to 0.850 in Model 2. Overall, the addition of eGFR_{diff} to UKBDRS resulted in a consistent but modest improvement in long-term discriminatory performance.

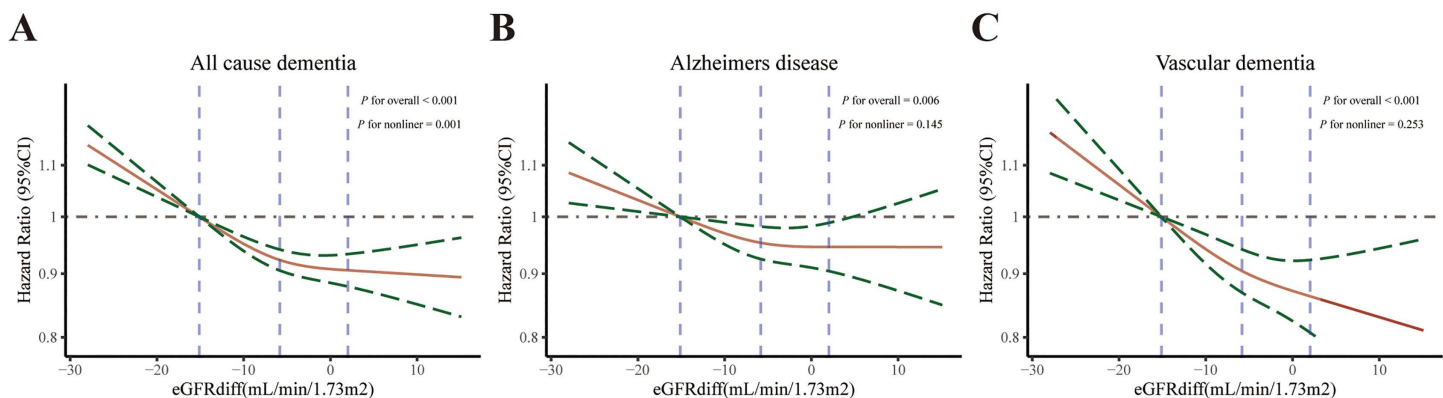


Fig 1. Dose-response relationship between eGFRdiff and All cause dementia(A), Alzheimers disease(B), or Vascular dementia(C). Restricted cubic spline was used to explore nonlinear associations, with three knots fixed at the quartiles for all smooth curves. Green line representing 95% Confidence interval. The HR was derived using Cox proportional hazard regression. Model were adjusted for eGFRcr_cys, Cho, LDL, education, smoking, drinking, physical activities, Townsend deprivation index (TDI), social isolate, hearing, eyesight, diabetes, hypertension, depression, and obesity.

<https://doi.org/10.1371/journal.pone.0344566.g001>

Association of dementia with neuroimaging changes and cognitive functions

A higher z-score of the eGFR_{diff} was significantly associated with greater total brain ($\beta = 0.010$, 95% CI, 0.001–0.019) and gray matter ($\beta = 0.024$, 95% CI, 0.016–0.033) volumes and lower WMH volumes ($\beta = -0.041$, 95% CI, -0.051 to -0.031). However, no significant associations were detected between the eGFR_{diff} and hippocampal volume, whether left ($\beta = -0.00$, 95% CI, -0.01 to 0.01) or right hippocampal volume ($\beta = -0.00$, 95% CI, -0.01 to 0.01). For cognitive function, the z-score of eGFR_{diff} showed no significant correlations with the Trail Making Test A ($\beta = -0.011$, 95% CI, -0.020 to 0.001), whereas a slight negative correlation was observed for the Trail Making Test B ($\beta = -0.015$, 95% CI, -0.024 to 0.005). In contrast, a slight positive correlation was observed between the eGFR_{diff} z-score and performance in several cognitive domains, including verbal and numerical reasoning ($\beta = 0.019$, 95% CI, 0.014–0.024), working memory ($\beta = 0.025$, 95% CI, 0.015–0.034), complex processing speed ($\beta = 0.031$, 95% CI, 0.022–0.039), verbal declarative memory ($\beta = 0.025$, 95% CI, 0.016–0.035), and non-verbal reasoning ($\beta = 0.014$, 95% CI, 0.005–0.023) (Table 3).

Discussion

Summary of findings

This large, population-based prospective cohort study revealed significant associations between the intraindividual eGFR_{diff} and the risk of dementia, as well as neuroimaging changes and cognitive functions. An L-shaped relationship was observed between the eGFR_{diff} and ACD risk. The observed temporal sequence—baseline eGFR_{diff} preceding MRI markers—supports a directional association. Indeed, negative eGFR_{diff} was associated with reduced total brain and gray matter volumes, increased white matter hyperintensities, and worse cognitive performance in dementia-free participants. These alterations may reflect early manifestations of brain vulnerability [22]. Subgroup analyses revealed consistent associations across various demographic and genetic factors, with notable modifications observed according to APOE genotype and ethnicity. These findings highlight the potential of the eGFR_{diff} as an indicator of dementia.

Interpretation of the findings

These findings are consistent with previous research on the associations between reduced eGFR_{diff} and adverse clinical outcomes, including frailty, depression, sarcopenia, cardiovascular events, and mortality in cohorts such as the Systolic Blood Pressure Intervention Trial (SPRINT), the Cardiovascular Health Study (CHS), and the UKB [16,18,20,21,39]. An

A

All-cause dementia

Variable	Count	Percent		HR (95%CI)	P value	P for interaction
Overall	458668	100		0.93 (0.90 to 0.95)	<0.001	
APOE_genotype						0.01
non-e4 carriers	335956	74.1		0.91 (0.88 to 0.95)	<0.001	
e4 carriers	117668	25.9		0.93 (0.90 to 0.97)	<0.001	
PRS.Q						0.061
PRS low	226857	50		0.92 (0.88 to 0.95)	<0.001	
PRS high	226767	50		0.94 (0.91 to 0.97)	<0.001	
sex						0.494
female	249242	54.3		0.95 (0.92 to 0.98)	0.005	
male	209426	45.7		0.91 (0.88 to 0.94)	<0.001	
ethnic						0.034
Others	24540	5.4		1.04 (0.94 to 1.14)	0.476	
White	434128	94.6		0.92 (0.90 to 0.94)	<0.001	

0.7 0.8 0.9 1 1.1 1.2 1.3

B

Alzheimer's disease

Variable	Count	Percent		HR (95%CI)	P value	P for interaction
Overall	458668	100		0.95 (0.92 to 0.99)	0.006	
APOE_genotype						0.066
non-e4 carriers	335956	74.1		0.94 (0.89 to 0.99)	0.026	
e4 carriers	117668	25.9		0.96 (0.91 to 1.00)	0.066	
PRS.Q						0.461
PRS low	226857	50		0.95 (0.89 to 1.00)	0.069	
PRS high	226767	50		0.96 (0.91 to 1.00)	0.067	
sex						0.355
female	249242	54.3		0.95 (0.90 to 1.00)	0.047	
male	209426	45.7		0.96 (0.91 to 1.01)	0.085	
ethnic						0.219
Others	24540	5.4		1.08 (0.92 to 1.25)	0.346	
White	434128	94.6		0.94 (0.91 to 0.98)	0.002	

0.7 0.8 0.9 1 1.1 1.2 1.3

C

Vascular dementia

Variable	Count	Percent		HR (95%CI)	P value	P for interaction
Overall	458668	100		0.91 (0.86 to 0.95)	<0.001	
APOE_genotype						0.338
non-e4 carriers	335956	74.1		0.90 (0.84 to 0.96)	0.002	
e4 carriers	117668	25.9		0.91 (0.84 to 0.98)	0.014	
PRS.Q						0.725
PRS low	226857	50		0.93 (0.87 to 1.01)	0.075	
PRS high	226767	50		0.88 (0.83 to 0.95)	<0.001	
sex						0.085
female	249242	54.3		0.96 (0.89 to 1.04)	0.319	
male	209426	45.7		0.87 (0.82 to 0.93)	<0.001	
ethnic						0.003
Others	24540	5.4		1.29 (1.03 to 1.60)	0.023	
White	434128	94.6		0.89 (0.84 to 0.93)	<0.001	

0.7 0.8 0.9 1 1.1 1.2 1.3

Fig 2. Subgroup analyses of the associations of eGFRdiff with all-cause dementia(A), AD(B) and VaD(C). Model were adjusted for eGFRcr_cys, Cho, LDL, education, smoking, drinking, physical activities, Townsend deprivation index (TDI), social isolate, hearing, eyesight, diabetes, hypertension, depression, and obesity.

<https://doi.org/10.1371/journal.pone.0344566.g002>

Table 3. Association of z-score of difference in cystatin C- and creatinine-based estimated glomerular filtration rate with neuroimaging outcomes and cognitive function.

Z-score of Outcomes	Number	β (95%CI) ^a	p-value
Neuroimaging Measures			
Total Brain Volume	38596	0.010 (0.001 to 0.019)	0.037
Grey Matter Volume	38596	0.024 (0.016 to 0.033)	<0.001
White Matter Volume	38596	-0.011 (-0.022 to 0.000)	0.053
Left Hippocampal Volume	38581	0.005 (-0.006 to 0.016)	0.351
Right Hippocampal Volume	38581	0.005 (-0.005 to 0.016)	0.324
White Matter Hyperintensity Volume	37442	-0.041 (-0.051 to -0.031)	<0.001
Cognitive Test Measures			
Executive Function (Trail Making Test A)	49910	-0.011 (-0.020 to -0.001)	0.029
Executive Function (Trail Making Test B)	49910	-0.015 (-0.024 to -0.005)	0.003
Verbal & Numerical Reasoning (Fluid Intelligence)	148759	0.019 (0.014 to 0.024)	<0.001
Working Memory (Backward Digit Span Task)	47295	0.025 (0.015 to 0.034)	<0.001
Complex Processing Speed (Symbol Digit Substitution)	49518	0.031 (0.022 to 0.039)	<0.001
Verbal Declarative Memory (Paired Associate Learning)	49910	0.025 (0.016 to 0.035)	<0.001
Non Verbal Reasoning (Matrix Pattern Completion)	49461	0.014 (0.005 to 0.023)	0.003

CI, confidence interval; eGFR_{cr-cys}, estimated glomerular filtration rate calculated using both creatinine and cystatin C; eGFR_{diff}, the difference between creatinine-based estimated glomerular filtration rate; TDI, Townsend deprivation index; MET, metabolic equivalent; LDL-C, serum low-density lipoprotein cholesterol; Cho: serum cholesterol;

^a Imaging-related confounds (head size, headmotion, head and table position, and imaging center) were regressed out from the neuroimaging outcomes (whitematter hyperintensity[WMH] volumes were log-transformed). Models were adjusted for eGFR_{cr-cys}, Age, Cho, LDL, education, smoking, drinking, physical activities, Townsend deprivation index (TDI), social isolate, hearing, eyesight, diabetes, hypertension, depression, and obesity.

<https://doi.org/10.1371/journal.pone.0344566.t003>

L-shaped association between eGFR_{diff} and cognitive decline has also been reported in the CHARLS cohort, as well as for diabetic microvascular complications and depressive symptoms [17,19,40]. Our results extend this evidence by demonstrating that negative eGFR_{diff} is associated with higher risks of ACD, AD, and VaD, whereas positive eGFR_{diff} does not confer additional protection beyond the midrange level.

Potential mechanisms may differ by dementia subtype. In AD, eGFR_{diff} may partly reflect muscle-related processes, as prior studies have shown strong associations between eGFR_{diff}, muscle mass, and strength [16,41], and sarcopenia itself is a known risk factor for dementia [42]. However, eGFR_{diff} alone is not a specific biomarker for sarcopenia [43], suggesting that additional systemic pathways are likely involved. Another possible mechanism is selective renal filtration impairment, such as “shrunk pore syndrome,” which may reduce the clearance of middle-molecular-weight proteins, including amyloid- β isoforms [44,45]. For VaD, microvascular dysfunction may be more relevant, supported by the observed association between eGFR_{diff} and white matter hyperintensities, a marker of cerebral small vessel disease [46–48].

Importantly, eGFR_{diff} is strongly influenced by non-renal determinants and does not solely reflect true differences in glomerular filtration. Creatinine is affected by muscle mass and physical activity, whereas cystatin C is influenced by inflammation, adiposity, thyroid dysfunction, and medication use. Therefore, negative eGFR_{diff} may represent a composite of systemic conditions that are themselves risk factors for dementia. From an epidemiological perspective, eGFR_{diff} may function as an integrated marker of overall health status and biological aging rather than a kidney-specific indicator, which may explain its stronger associations with dementia-related outcomes than eGFR based on either biomarker alone. Accordingly, the observed associations likely reflect shared underlying pathophysiological pathways rather than a direct causal effect of renal dysfunction on dementia risk.

While we propose potential biological pathways linking $eGFR_{diff}$ to dementia subtypes, these mechanisms remain speculative. Our observational design limits our ability to draw definitive conclusions about causality or underlying pathophysiology, and experimental studies are needed to validate these hypotheses.

Clinical implications and recommendations

Several factors suggest that the $eGFR_{diff}$ might be considered a potential associative indicator that warrants further experimental validation, with implications for risk stratification and public health management. Although the improvement in AUC after adding $eGFR_{diff}$ to UKBDRS was modest, this finding is not unexpected given that UKBDRS already demonstrates strong baseline discrimination. Nevertheless, from an epidemiological and mechanistic perspective, the consistent associations of $eGFR_{diff}$ with dementia incidence, neuroimaging changes, and cognitive function suggest that $eGFR_{diff}$ reflects early systemic vulnerability relevant to neurodegeneration, even if its incremental contribution to prediction accuracy is limited. First, $eGFR_{diff}$ is a highly accessible metric, as both the U.S. National Kidney Foundation and the American Society of Nephrology recommend measuring both creatinine and cystatin C, with the eGFR calculated from these metrics being the most accurate estimate [49]. Second, a significant proportion of individuals exhibit substantial discordance between $eGFR_{cr}$ and $eGFR_{cys}$ values. UKB data indicate that over 40% of participants have differences exceeding 20% [13,50]. A 25-year longitudinal study further demonstrated that individuals whose baseline $eGFR_{cys}$ values were more than 30% lower than their corresponding $eGFR_{cr}$ values tended to maintain this discrepancy over time [51]. These differences may be attributed to the influence of muscle mass and medication use on creatinine-based estimates, whereas cystatin C is affected by non-GFR determinants such as inflammation, steroid therapy, and thyroid dysfunction [52].

Given the observed ethnic heterogeneity in effect estimates, particularly the significant interaction for VaD, $eGFR_{diff}$ -based risk assessment tools should not be directly implemented in diverse populations without prior validation. The differential associations may reflect varying prevalence of comorbidities, genetic determinants of cystatin C metabolism, or sociocultural factors affecting kidney function across ethnic groups. Future research should prioritize inclusion of underrepresented minorities to ensure equitable translation of these findings.

Given the established role of combined creatinine and cystatin C assessment in clinical nephrology and the high prevalence of discordant estimates in the general population, incorporating $eGFR_{diff}$ into routine assessment may help identify individuals with elevated systemic vulnerability who may benefit from closer cognitive monitoring and early preventive strategies.

Limitations

This study has several limitations. First, the observational nature of the study precludes direct causal inferences, and the predominantly white study population limits the generalizability of findings to other racial groups and younger individuals. Second, The study population was predominantly of White ethnicity (94.6%), reflecting the demographic composition of the UK Biobank cohort. This significant limitation restricts the generalizability of our findings to more ethnically diverse populations. Our findings should be interpreted with caution when applied to non-White populations, and validation in diverse cohorts is essential before considering clinical implementation in heterogeneous populations. Third, reliance on hospital records for dementia diagnosis may affect the sensitivity and specificity of case identification. Fourth, because $eGFR_{diff}$ is substantially affected by non-renal factors, it may capture overall health status rather than isolated kidney function. Although this characteristic supports its use as a global risk marker, it limits mechanistic interpretation and precludes causal inference regarding renal pathways in dementia development. Fifth, the optimal $eGFR_{diff}$ threshold reported herein is data-driven and exploratory; its generalizability to unselected populations and its clinical utility beyond risk stratification remain to be established. Because of the observational nature of this study, these findings support but do not prove a causal role of $eGFR_{diff}$ in dementia pathogenesis. Despite these limitations, this study provides valuable insights into the potential role of the $eGFR_{diff}$ as an early indicator of dementia risk, neuroimaging abnormalities, and cognitive decline..

Conclusion

This study revealed a strong associations between the $eGFR_{diff}$ and the risk of dementia, adverse neuroimaging outcomes, and cognitive decline in a predominantly White UK population. Given that a significant proportion of the study population exhibited a negative $eGFR_{diff}$, the $eGFR_{diff}$ might be considered a potential associative indicator for dementia, with implications for risk stratification and public health management. Future research should focus on elucidating the underlying mechanism and evaluating its clinical applicability in dementia prevention.

Supporting information

S1 File. S1 Fig. Flow diagram of analyses. Flow diagram of analyses. ^aSensitivity analysis was conducted in this population using multiple imputation to account for missing data on the exposure and covariates or removing low-eGFR participations. S2 Fig. Correlation matrix of kidney function markers. Hexbin plot of the relation between $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{diff}$ at baseline. (A) Correlation between $eGFR_{cr}$ and $eGFR_{cys}$. (B) Correlation between $eGFR_{cr}$ and $eGFR_{diff}$. (C) Correlation between $eGFR_{cys}$ and $eGFR_{diff}$. S3 Fig. Survival curves and proportional hazards assessment. Kaplan-Meier survival curves using time-scale and scatter plot of the scaled Schoenfeld residuals for $eGFR_{diff}$ and all cause dementia(A), Alzheimer's disease(B) and vascular dementia(C). S4 Fig. Nonlinear dose-response relationships. Dose-response relationship between $eGFR_{ratio}$ (A to C) and All cause dementia, Alzheimer's disease, or Vascular dementia. Restricted cubic spline was used to explore nonlinear associations, with three knots fixed at the quartiles for all smooth curves. Green line representing 95% Confidence interval. The HR was derived using Cox proportional hazard regression. Model were adjusted for $eGFR_{cr_cys}$, Cho, LDL, education, smoking, drinking, physical activities, Townsend deprivation index (TDI), social isolate, hearing, eyesight, diabetes, hypertension, depression, and obesity. S5 Fig. Sensitivity analyses of eGFR measures. Associations between $eGFR_{diff}$ or $eGFR_{ratio}$ (z-score) and incident dementia. (A) Model 1 were adjusted for Cho, LDL, education, smoking, drinking, physical activities, Townsend deprivation index (TDI), social isolate, hearing, eyesight, diabetes, hypertension, depression, and obesity. (B) Model 2 were further adjusted for $eGFR_{cr_cys}$. S6 Fig. Risk stratification by optimal $eGFR_{diff}$ cut-off. Kaplan-Meier curves for incident all-cause dementia according to high- and low-risk groups defined by the optimal cut-off value of $eGFR_{diff}$ (-8.813) derived from maximally selected rank statistics. S7 Fig. Incremental predictive value of $eGFR_{diff}$. Time-dependent ROC curves comparing discrimination performance of UKBDRS alone versus UKBDRS combined with $eGFR_{diff}$ at 5, 10, and 15 years of follow-up. S1 Table. Association between $eGFR_{diff}$ and dementia after multiple imputation. Hazard ratios (95% CI) for categorical and continuous $eGFR_{diff}$ with all-cause dementia, Alzheimer's disease, and vascular dementia following multiple imputation of missing covariates. S2 Table. Association between $eGFR_{diff}$ and dementia excluding low eGFR participants. Sensitivity analysis showing hazard ratios for $eGFR_{diff}$ and dementia outcomes after excluding participants with $eGFR < 60$ ml/min/1.73m². S3 Table. Association between $eGFR_{ratio}$ and incident dementia. Hazard ratios for the association between $eGFR_{ratio}$ (quartiles and continuous) with all-cause dementia, Alzheimer's disease, and vascular dementia. S4 Table. Stratified analysis in participants with diabetes. Association between $eGFR_{diff}$ (categorical and continuous) and incident dementia outcomes among participants with diabetes at baseline. S5 Table. Stratified analysis in participants with hypertension. Association between $eGFR_{diff}$ (categorical and continuous) and incident dementia outcomes among participants with hypertension at baseline. S6 Table. Stratified analysis in participants with depression. Association between $eGFR_{diff}$ (categorical and continuous) and incident dementia outcomes among participants with depression at baseline. S7 Table. Negative control analysis using traumatic injury. Association between $eGFR_{diff}$ and incident traumatic injury (ICD-10 S00-T35, T66-78) as a negative control outcome to assess potential residual confounding. S1 Method. Genetic risk assessment methodology and Survival analysis and model discrimination methods. S1 Code. R Code for analyses of this study. (ZIP)

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References

1. Avan A, Hachinski V. Global, regional, and national trends of dementia incidence and risk factors, 1990–2019: A Global Burden of Disease study. *Alzheimers Dement*. 2023;19(4):1281–91. <https://doi.org/10.1002/alz.12764> PMID: [36044376](https://pubmed.ncbi.nlm.nih.gov/36044376/)
2. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019). Seattle, United States: Institute for Health Metrics and Evaluation (IHME). 2020. <https://www.healthdata.org/research-analysis/gbd>
3. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. *Biomed Res Int*. 2014;2014:908915. <https://doi.org/10.1155/2014/908915> PMID: [25089278](https://pubmed.ncbi.nlm.nih.gov/25089278/)
4. Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. 2024;404(10452):572–628. [https://doi.org/10.1016/S0140-6736\(24\)01296-0](https://doi.org/10.1016/S0140-6736(24)01296-0) PMID: [39096926](https://pubmed.ncbi.nlm.nih.gov/39096926/)
5. Newby D, Orgeta V, Marshall CR, Lourida I, Albertyn CP, Tamburin S, et al. Artificial intelligence for dementia prevention. *Alzheimers Dement*. 2023;19(12):5952–69. <https://doi.org/10.1002/alz.13463> PMID: [37837420](https://pubmed.ncbi.nlm.nih.gov/37837420/)
6. Wang S, Wang J, Dove A, Guo J, Yang W, Qi X, et al. Association of impaired kidney function with dementia and brain pathologies: A community-based cohort study. *Alzheimers Dement*. 2023;19(7):2765–73. <https://doi.org/10.1002/alz.12910> PMID: [36571791](https://pubmed.ncbi.nlm.nih.gov/36571791/)
7. Chu NM, Hong J, Harasemiw O, Chen X, Fowler KJ, Dasgupta I, et al. Chronic kidney disease, physical activity and cognitive function in older adults—results from the National Health and Nutrition Examination Survey (2011–2014). *Nephrol Dial Transplant*. 2022;37(11):2180–9. <https://doi.org/10.1093/ndt/gfab338> PMID: [34850174](https://pubmed.ncbi.nlm.nih.gov/34850174/)
8. Helmer C, Stengel B, Metzger M, Froissart M, Massy Z-A, Tzourio C, et al. Chronic kidney disease, cognitive decline, and incident dementia: The 3C Study. *Neurology*. 2011;77(23):2043–51. <https://doi.org/10.1212/WNL.0b013e31823b4765> PMID: [22116945](https://pubmed.ncbi.nlm.nih.gov/22116945/)
9. Stocker H, Beyer L, Trares K, Perna L, Rujescu D, Holczek B, et al. Association of kidney function with development of alzheimer disease and other dementias and dementia-related blood biomarkers. *JAMA Netw Open*. 2023;6(1):e2252387. <https://doi.org/10.1001/jamanetworkopen.2022.52387> PMID: [36692879](https://pubmed.ncbi.nlm.nih.gov/36692879/)
10. O'Hare AM, Walker R, Haneuse S, Crane PK, McCormick WC, Bowen JD, et al. Relationship between longitudinal measures of renal function and onset of dementia in a community cohort of older adults. *J Am Geriatr Soc*. 2012;60(12):2215–22. <https://doi.org/10.1111/j.1532-5415.2012.04238.x> PMID: [23231548](https://pubmed.ncbi.nlm.nih.gov/23231548/)
11. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin c-based equations to estimate GFR without race. *N Engl J Med*. 2021;385(19):1737–49. <https://doi.org/10.1056/NEJMoa2102953> PMID: [34554658](https://pubmed.ncbi.nlm.nih.gov/34554658/)
12. Scheppach JB, Coresh J, Wu A, Gottesman RF, Mosley TH, Knopman DS, et al. Albuminuria and estimated GFR as risk factors for dementia in midlife and older age: Findings from the ARIC study. *Am J Kidney Dis*. 2020;76(6):775–83. <https://doi.org/10.1053/j.ajkd.2020.03.015> PMID: [32428540](https://pubmed.ncbi.nlm.nih.gov/32428540/)
13. Lees JS, Welsh CE, Celis-Morales CA, Mackay D, Lewsey J, Gray SR, et al. Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. *Nat Med*. 2019;25(11):1753–60. <https://doi.org/10.1038/s41591-019-0627-8> PMID: [31700174](https://pubmed.ncbi.nlm.nih.gov/31700174/)
14. Kang MW, Park S, Lee S, Lee Y, Cho S, Han K, et al. Glomerular hyperfiltration is associated with dementia: A nationwide population-based study. *PLoS One*. 2020;15(1):e0228361. <https://doi.org/10.1371/journal.pone.0228361> PMID: [31990949](https://pubmed.ncbi.nlm.nih.gov/31990949/)
15. Sang D, Tao J, Song W, Zhang Q, Wu S, Geng W. Comparison of the correlation of creatinine- and cystatin C-Based estimated GFR and their differences with new-onset heart failure in a community-based population with type 2 diabetes. *Diabetol Metab Syndr*. 2024;16(1):225. <https://doi.org/10.1186/s13098-024-01461-2> PMID: [39267159](https://pubmed.ncbi.nlm.nih.gov/39267159/)

16. Potok OA, Ix JH, Shlipak MG, Bansal N, Katz R, Kritchevsky SB, et al. Cystatin C- and creatinine-based glomerular filtration rate estimation differences and muscle quantity and functional status in older adults: The health, aging, and body composition study. *Kidney Med.* 2022;4(3):100416. <https://doi.org/10.1016/j.xkme.2022.100416> PMID: 35386603
17. Li Q, Song C, Zhou H, Li J, Chen M. Sex differences in the relationship of intraindividual difference in estimated glomerular filtration rate by cystatin C and creatinine and depressive symptoms among middle-aged and older adults in China. *J Affect Disord.* 2025;369:103–9. <https://doi.org/10.1016/j.jad.2024.09.169> PMID: 39341290
18. Kim H, Park JT, Lee J, Jung JY, Lee K-B, Kim Y-H, et al. The difference between cystatin C- and creatinine-based eGFR is associated with adverse cardiovascular outcome in patients with chronic kidney disease. *Atherosclerosis.* 2021;335:53–61. <https://doi.org/10.1016/j.atherosclerosis.2021.08.036> PMID: 34571286
19. He D, Gao B, Wang J, Yang C, Zhao M-H, Zhang L. The difference between cystatin C- and creatinine-based estimated glomerular filtration rate and risk of diabetic microvascular complications among adults with diabetes: A population-based cohort study. *Diabetes Care.* 2024;47(5):873–80. <https://doi.org/10.2337/dc23-2364> PMID: 38470988
20. Potok OA, Ix JH, Shlipak MG, Katz R, Hawfield AT, Rocco MV, et al. The Difference Between Cystatin C- and creatinine-based estimated gfr and associations with frailty and adverse outcomes: A Cohort Analysis of the Systolic Blood Pressure Intervention Trial (SPRINT). *Am J Kidney Dis.* 2020;76(6):765–74. <https://doi.org/10.1053/j.ajkd.2020.05.017> PMID: 32682697
21. Potok OA, Katz R, Bansal N, Siscovick DS, Odden MC, Ix JH, et al. The difference between cystatin C- and creatinine-based estimated GFR and incident frailty: An analysis of the cardiovascular health study (CHS). *Am J Kidney Dis.* 2020;76(6):896–8. <https://doi.org/10.1053/j.ajkd.2020.05.018> PMID: 32682698
22. Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* 2013;12(2):207–16. [https://doi.org/10.1016/S1474-4422\(12\)70291-0](https://doi.org/10.1016/S1474-4422(12)70291-0) PMID: 23332364
23. Littlejohns TJ, Holliday J, Gibson LM, Garratt S, Oesingmann N, Alfaro-Almagro F, et al. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nat Commun.* 2020;11(1):2624. <https://doi.org/10.1038/s41467-020-15948-9> PMID: 32457287
24. Alfaro-Almagro F, Jenkinson M, Bangerter NK, Andersson JLR, Griffanti L, Douaud G, et al. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage.* 2018;166:400–24. <https://doi.org/10.1016/j.neuroimage.2017.10.034> PMID: 29079522
25. Fawns-Ritchie C, Deary IJ. Reliability and validity of the UK Biobank cognitive tests. *PLoS One.* 2020;15(4):e0231627. <https://doi.org/10.1371/journal.pone.0231627> PMID: 32310977
26. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012;367(1):20–9. <https://doi.org/10.1056/NEJMoa1114248> PMID: 22762315
27. Grubb A. Shrunken pore syndrome - a common kidney disorder with high mortality. Diagnosis, prevalence, pathophysiology and treatment options. *Clin Biochem.* 2020;83:12–20. <https://doi.org/10.1016/j.clinbiochem.2020.06.002> PMID: 32544475
28. Sommerlad A, Perera G, Singh-Manoux A, Lewis G, Stewart R, Livingston G. Accuracy of general hospital dementia diagnoses in England: Sensitivity, specificity, and predictors of diagnostic accuracy 2008–2016. *Alzheimers Dement.* 2018;14(7):933–43. <https://doi.org/10.1016/j.jalz.2018.02.012> PMID: 29703698
29. Biobank U. Algorithmically defined outcomes (ADOs). https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/alg_outcome_main.pdf. 2022.
30. Xiang Y, Xu H, Chen H, Tang D, Huang Z, Zhang Y, et al. Tea consumption and attenuation of biological aging: A longitudinal analysis from two cohort studies. *Lancet Reg Health West Pac.* 2023;42:100955. <https://doi.org/10.1016/j.lanwpc.2023.100955> PMID: 38075587
31. Tang R, Wang X, Li X, Ma H, Liang Z, Heianza Y, et al. Adherence to Life's Essential 8 and incident chronic kidney disease: A prospective study of 147,988 UK Biobank participants. *Am J Clin Nutr.* 2023;118(4):804–11. <https://doi.org/10.1016/j.ajcnut.2023.08.007> PMID: 37604298
32. Committee IR others. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)-short and long forms. 2005. <https://www.ipaq.ki.se/scoring>
33. Hendriks S, Ranson JM, Peetoom K, Lourida I, Tai XY, de Vugt M, et al. Risk Factors for young-onset dementia in the UK Biobank. *JAMA Neurol.* 2024;81(2):134–42. <https://doi.org/10.1001/jamaneurol.2023.4929> PMID: 38147328
34. Shang X, Zhu Z, Wang W, Ha J, He M. The association between vision impairment and incidence of dementia and cognitive impairment: A systematic review and meta-analysis. *Ophthalmology.* 2021;128(8):1135–49. <https://doi.org/10.1016/j.ophtha.2020.12.029> PMID: 33422559
35. Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *J Stat Soft.* 2011;45(3). <https://doi.org/10.18637/jss.v045.i03>
36. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604–12. <https://doi.org/10.7326/0003-4819-150-9-200905050-00006> PMID: 19414839
37. Alders P, Kok A, van Zutphen EM, Claassen JAHR, Deeg DJH. The effect of sleep disturbances on the incidence of dementia for varying lag times. *J Prev Alzheimers Dis.* 2025;12(2):100024. <https://doi.org/10.1016/j.tipad.2024.100024> PMID: 39863328

38. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–7. [https://doi.org/10.1016/S0140-6736\(07\)61602-X](https://doi.org/10.1016/S0140-6736(07)61602-X) PMID: [18064739](#)
39. Heo GY, Koh HB, Jung C-Y, Park JT, Han SH, Yoo T-H, et al. Difference between estimated GFR based on cystatin C versus creatinine and incident atrial fibrillation: A cohort study of the UK Biobank. *Am J Kidney Dis*. 2024;83(6):729–738.e1. <https://doi.org/10.1053/j.ajkd.2023.11.004> PMID: [38171411](#)
40. Wang J, Liu Y, Jin R, Zhao X, Wu Z, Han Z, et al. Intraindividual difference in estimated GFR by creatinine and cystatin C, cognitive trajectories and motoric cognitive risk syndrome. *Nephrol Dial Transplant*. 2024;39(5):860–72. <https://doi.org/10.1093/ndt/gfad234> PMID: [37930847](#)
41. Yuan JH, Rifkin DE, Ginsberg C, Cawthon PM, Kado DM, Bauer SR, et al. Difference between kidney function by cystatin C versus creatinine and association with muscle mass and frailty. *J Am Geriatr Soc*. 2024;72(10):3163–70. <https://doi.org/10.1111/jgs.19014> PMID: [38819605](#)
42. Hu Y, Peng W, Ren R, Wang Y, Wang G. Sarcopenia and mild cognitive impairment among elderly adults: The first longitudinal evidence from CHARLS. *J Cachexia Sarcopenia Muscle*. 2022;13(6):2944–52. <https://doi.org/10.1002/jcsm.13081> PMID: [36058563](#)
43. Jang JY, Shin HE, Won CW, Kim M. Comparison of the serum creatinine- and cystatin-C-based indices as screening biomarkers for sarcopenia in community-dwelling older adults. *Arch Gerontol Geriatr*. 2023;115:105207. <https://doi.org/10.1016/j.archger.2023.105207> PMID: [37776755](#)
44. Malmgren L, Öberg C, den Bakker E, Leion F, Siódmiak J, Åkesson A, et al. The complexity of kidney disease and diagnosing it - cystatin C, selective glomerular hypofiltration syndromes and proteome regulation. *J Intern Med*. 2023;293(3):293–308. <https://doi.org/10.1111/joim.13589> PMID: [36385445](#)
45. Motolese F, Norata D, Iaccarino G, Sapio E, Capone F. The effect of creatinine level on amyloid- β and tau plasma concentrations in a cohort of Alzheimer's disease patients without kidney disease. *Behav Brain Res*. 2025;477:115289. <https://doi.org/10.1016/j.bbr.2024.115289> PMID: [39396574](#)
46. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822–38. [https://doi.org/10.1016/S1474-4422\(13\)70124-8](https://doi.org/10.1016/S1474-4422(13)70124-8) PMID: [23867200](#)
47. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9(7):689–701. [https://doi.org/10.1016/S1474-4422\(10\)70104-6](https://doi.org/10.1016/S1474-4422(10)70104-6) PMID: [20610345](#)
48. de Havenon A, Gottesman RF, Williamson JD, Rost N, Sharma R, Li V, et al. White matter hyperintensity on MRI and plasma A β 42/40 ratio additively increase the risk of cognitive impairment in hypertensive adults. *Alzheimers Dement*. 2024;20(10):6810–9. <https://doi.org/10.1002/alz.14126> PMID: [39229896](#)
49. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, et al. A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task force on reassessing the inclusion of race in diagnosing kidney disease. *JASN*. 2021;32(12):2994–3015. <https://doi.org/10.1681/asn.2021070988>
50. Grubb A, Lindström V, Jonsson M, Bäck S-E, Åhlund T, Rippe B, et al. Reduction in glomerular pore size is not restricted to pregnant women. Evidence for a new syndrome: "Shrunken pore syndrome". *Scand J Clin Lab Invest*. 2015;75(4):333–40. <https://doi.org/10.3109/00365513.2015.1025427> PMID: [25919022](#)
51. Farrington DK, Surapaneni A, Matsushita K, Seegmiller JC, Coresh J, Grams ME. Discrepancies between Cystatin C-Based and Creatinine-Based eGFR. *Clin J Am Soc Nephrol*. 2023;18(9):1143–52. <https://doi.org/10.2215/CJN.0000000000000217> PMID: [37339177](#)
52. Inker LA, Titan S. Measurement and estimation of GFR for use in clinical practice: Core curriculum 2021. *Am J Kidney Dis*. 2021;78(5):736–49. <https://doi.org/10.1053/j.ajkd.2021.04.016> PMID: [34518032](#)