Higher blood urea nitrogen is associated with increased risk of incident diabetes mellitus

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Experimental evidence suggests that higher levels of urea may increase insulin resistance and suppress insulin secretion. However, whether higher levels of blood urea nitrogen (BUN) are associated with increased risk of incident diabetes mellitus in humans is not known. To study this, we built a national cohort of 1,337,452 United States Veterans without diabetes to characterize the association of BUN and risk of incident diabetes. Over a median follow-up of 4.93 years, there were 172,913 cases of incident diabetes. In joint risk models of estimated glomerular filtration rate (eGFR) and BUN. there was no association between eGFR and the risk of incident diabetes in those with a BUN of 25 mg/dl or less. However, the risk was significantly increased in those with a BUN over 25 mg/dl at all eGFR levels, even in those with an eGFR of 60 ml/min/1.73m^2 or more (hazard ratio 1.27; confidence interval 1.24-1.31). The risk of incident diabetes was highest in those with BUN over 25 mg/dL and an eGFR under 15 ml/min/1.73m^2 (1.68; 1.51-1.87). Spline analyses of the relationship between BUN and risk of incident diabetes showed that risk was progressively higher as BUN increased. In models where eGFR was included as a continuous covariate, compared to a BUN of 25 mg/dl or less, a BUN over 25 mg/dl was associated with increased risk of incident diabetes (1.23; 1.21-1.25). Every 10 ml/min/1.73m^2 decrease in eGFR was not associated with risk of incident diabetes (1.00; 1.00-1.01). Two-stage residual inclusion analyses showed that, independent of the impact of eGFR, every 10 mg/dL increase in BUN concentration was associated with increased risk of incident diabetes (1.15; 1.14-1.16). Thus, higher levels of BUN are associated with increased risk of incident diabetes mellitus.

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Chronic kidney disease (CKD) is characterized by disturbances in glucose and insulin homeostasis.[1] In a cohort of 4680 participants without diabetes mellitus in the Cardiovascular Health Study, Pham *et al.*[2] reported that a decreased estimated glomerular filtration rate (eGFR) is associated with increased insulin resistance; however, over a median follow-up of 12 years, participants with a decreased eGFR did not have an increased risk of incident diabetes mellitus. It was noted that the majority of cohort participants had mild CKD, and the number of participants with an eGFR <45 ml/min per 1.73 m^2 was small ($N = 282$), which may not have allowed a more nuanced characterization of the risk of diabetes mellitus in those with a very low eGFR. In an elegant subsequent study of 59 participants with nondiabetic CKD (mean eGFR, 37.6 ml/min per 1.73 m^2) and 39 healthy controls, de Boer *et al.* reported that those with CKD had lower insulin sensitivity, reduced insulin clearance, and inadequate augmentation of insulin secretion.[3,4] The investigators suggested that the combination of insulin resistance and an inability to adequately augment insulin secretion led to the observation of a higher prevalence of glucose intolerance in moderate to severe CKD.

Experimental evidence identifies urea as a putative culprit of reduced insulin sensitivity and defective insulin secretion.[5,6] Studies by D'Apolito *et al.*[5] suggest that cultured adipocytes treated with urea (at disease-relevant concentrations) exhibited decreased insulin sensitivity. In a mouse model of surgically induced kidney failure, uremic mice displayed insulin resistance and glucose intolerance, and urea infusion produced the same degree of insulin resistance in normal mice.[5] Recent seminal observations by Koppe *et al.*[6] and Thomas *et al.*[7] suggest that defective insulin secretion in CKD is mechanistically caused by elevated levels of circulating urea, a condition that becomes manifest in advanced stages of CKD.

The disturbances of glucose and insulin homeostasis in CKD are complex and represent 2 opposing forces at play.

On the one hand, CKD decreases insulin sensitivity (and increases insulin resistance) and, in advanced stages, results in beta-cell dysfunction and defective insulin secretion.[8] On the other hand, CKD leads to decreased insulin clearance, thus prolonging its half-life.[1,9] The balance of these 2 opposing forces shapes the state of glucose metabolism and ultimately the risk of diabetes mellitus in any individual patient. We hypothesized that as CKD progresses and blood urea nitrogen (BUN) increases, both reduced insulin sensitivity and defective insulin secretion become more pronounced and result in a state of clinically evident diabetes mellitus and that, congruent with the experimental evidence of urea suppressing insulin sensitivity and insulin secretion, higher levels of BUN are associated with an increased risk of incident diabetes mellitus. Taking a big data approach, we used the US Department of Veterans Affairs (VA) databases to build a national cohort of 1,337,452 US veterans without diabetes mellitus and followed them over time to characterize the association of BUN and the risk of incident diabetes mellitus.

RESULTS

There were 1,337,452 cohort participants followed for a median of 4.93 years (interquartile range, 4.93–4.93). Table 1 details the demographic and health characteristics of the overall cohort by BUN category (≤25 and >25 mg/dl) at time of cohort entry (T_0). Supplementary Table S1 describes baseline characteristics by eGFR category. Overall, cohort participants were mostly of white race and male sex (Table 1). Cohort participants had an average first eGFR and first BUN level of 75.55 ± 19.94 ml/min per 1.72 m^2 and 16.78 ± 7.04 mg/dl, respectively (Table 1). There were 172,913 (12.93%) incident cases of diabetes in the overall cohort. In inverse probability weighting analyses (which account for the uneven probability of experiencing competing risk in BUN categories) (weighted N = 1,340,998), there were 210,873 (15.73%) cases of incident diabetes: 23,649 (19.85%) in those with a BUN level >25 mg/dl and 187,224 (15.32%) in those with a BUN level ≤25 mg/dl (Table 1). The 5-year diabetes-free survival probability by time-updated eGFR category and time-updated BUN category are presented in Figures 1 and 2, respectively.

Association between time-updated eGFR and the risk of incident diabetes mellitus

In Cox survival models adjusted for age, race, sex, and time-varying variables including body mass index (BMI), serum carbon dioxide, albuminuria, frequency of outpatient encounters, frequency of hospitalizations, and relevant comorbidities and health characteristics, compared with those with an eGFR ≥60 ml/min per 1.73 m^2, there was a gradual increase in the risk of incident diabetes mellitus with a decreasing eGFR (Table 2). Risk was pronounced in those with an eGFR <30 and ≥15 ml/min per 1.73 m^2 and those with an eGFR <15 ml/min per 1.73 m^2 with a hazard ratio (HR) of 1.17, 95% confidence interval (CI) 1.12–1.22, and an HR of 1.64, 95% CI 1.48–1.82, respectively (Table 2). Spline analysis of the relationship between the eGFR and the risk of incident diabetes mellitus suggested an exponential relationship in which risk progressively increased as eGFR decreased (Figure 3).

Association between time-updated BUN and the risk of incident diabetes mellitus

Using a big data approach, we tested the question of whether elevated levels of urea are associated with an increased risk of incident diabetes mellitus. In a joint risk model (of eGFR and BUN), we examined the risk of incident diabetes by BUN and eGFR category (Table 3). In cohort participants with low BUN (≤25 mg/dl), there was no significant relationship between the eGFR and the risk of incident diabetes in any eGFR category. In cohort participants with BUN >25 mg/dl, the risk of incident diabetes was significantly increased at all eGFR levels, even in those with an eGFR ≥60 ml/min per 1.73 m^2 (HR, 1.27; 95% CI 1.24–1.31) (Table 3). The risk of incident diabetes was highest in those with BUN >25 mg/dl and an eGFR <15 ml/min per 1.73 m^2 (HR, 1.68; 95% CI 1.51–1.87) (Table 3). A joint risk model with BUN categorized in quintiles yielded consistent findings (Supplementary Table S2). A spline analysis of the relationship between BUN and the risk of incident diabetes showed that the risk of incident diabetes was progressively higher as BUN increased (Figure 4).

In models in which eGFR was included as a continuous covariate, compared with BUN ≤25 mg/dl, BUN >25 mg/dl was associated with an increased risk of incident diabetes mellitus (HR, 1.23; 95% CI 1.21–1.25). In the same model, every 10-ml/min per 1.73 m^2 increase in the eGFR was not associated with the risk of incident diabetes mellitus (HR, 1.00; 95% CI 1.00–1.01). Spline analysis, which included both the eGFR and BUN, showed that although the risk of incident diabetes mellitus increased with increased BUN concentrations, the risk was decreased with decreased eGFR (Figure 5). Because the eGFR and BUN are inherently correlated, we applied a 2-stage residual inclusion method to account for this correlation and evaluate the independent impact of BUN on the risk of incident diabetes.[10] Results showed that, after accounting for the effect of eGFR and its correlation with BUN, every 10 mg/dl increase in BUN concentration was associated with a significant increase in the risk of incident diabetes mellitus (HR, 1.15; 95% CI 1.14–1.16). However, independent of the impact of BUN, every 10 ml/min per 1.73 m^2 increase of eGFR yielded no significant change in the risk of diabetes mellitus (HR, 1.01; 95% CI 1.01–1.01).

Formal interaction analyses were undertaken and showed that increasing age attenuated the association of BUN and the risk of incident diabetes (P value for interaction <0.001). BUN >25 mg/dl was more strongly associated with an increased risk of diabetes among cohort participants who were younger than the median age of the overall cohort (65.1 years

Table 1 | Baseline characteristics of the overall cohort and according to BUN category (≤25 and >25 mg/dl) at time of cohort entry (T_0)

Variables	Overall (*N* = 1,337,452)	BUN ≤25 mg/dl (*N* = 1,220,171, 91.23%)	BUN >25 mg/dl (*N* = 117,281, 8.77%)
Age, yr (SD)	65.74 (13.38)	64.67 (13.16)	76.94 (10.14)
Race, *N* (%)			
White	1,099,079 (82.18)	992,966 (81.38)	106,113 (90.48)
Black	181,133 (13.54)	173,859 (14.25)	7274 (6.20)
Other	57,240 (4.28)	53,346 (4.37)	3894 (3.32)
Sex, *N* (%)			
Male	1,264,325 (94.53)	1,149,488 (94.21)	114,837 (97.92)
Female	73,127 (5.47)	70,683 (5.79)	2,444 (2.08)
T_0 eGFR, ml/min per 1.73 m^2 (SD)	75.55 (19.94)	78.15 (18.17)	48.57 (17.41)
T_0 BUN, mg/dl (SD)	16.78 (7.04)	15.29 (4.62)	32.33 (8.88)
T_0 serum carbon dioxide, MEq/l (SD)	27.22 (3.04)	27.30 (2.99)	26.32 (3.42)
Chronic lung disease, *N* (%)	336,088 (25.13)	303,398 (24.89)	32,690 (27.87)
Peripheral artery disease, *N* (%)	50,979 (3.81)	42,376 (3.47)	8603 (7.34)
Cardiovascular disease, *N* (%)	413,788 (30.94)	352,997 (28.93)	60,791 (51.83)
Cerebrovascular disease, *N* (%)	8170 (0.61)	6777 (0.56)	1393 (1.19)
Dementia, *N* (%)	82,005 (6.13)	70,717 (5.80)	11,288 (9.62)
Hyperlipidemia, *N* (%)	921,738 (68.92)	831,241 (68.12)	90,497 (77.16)
Hepatitis C, *N* (%)	79,971 (5.98)	76,700 (6.29)	3271 (2.79)
HIV, *N* (%)	4437 (0.33)	4264 (0.35)	173 (0.15)
Cancer, *N* (%)	239,164 (17.88)	207,802 (17.03)	31,362 (26.74)
Albuminuria, (%)	76,042 (5.69)	61,352 (5.03)	14,690 (12.53)
Frequency of outpatient encounters, *N* (%)			
Low (≤4.0 times/yr)	337,451 (25.23)	308,736 (25.30)	28,715 (24.48)
Medium to low (4.0–7.2 times/yr)	336,795 (25.18)	307,167 (25.17)	29,628 (25.26)
Medium-high (7.2–13.2 times/yr)	332,855 (24.89)	304,383 (24.95)	28,472 (24.28)
High (>13.2 times/yr)	330,351 (24.70)	299,885 (24.58)	30,466 (25.98)
Frequency of hospitalizations, *N* (%)			
Never	1,067,845 (79.84)	975,889 (79.98)	91,956 (78.41)
Low (1 time)	147,949 (11.06)	135,621 (11.11)	12,328 (10.51)
Medium (2 times)	56,232 (4.20)	50,607 (4.15)	5625 (4.80)
High (>2 times)	65,426 (4.89)	58,054 (4.76)	7372 (6.29)
Body mass index, *N* (%)			
Underweight	20,197 (1.51)	17,989 (1.47)	2208 (1.88)
Normal	336,511 (25.16)	301,389 (24.70)	35,122 (29.95)
Overweight	550,136 (41.13)	501,191 (41.08)	48,945 (41.73)
Obese	430,608 (32.20)	399,602 (32.75)	31,006 (26.44)
Use of medications that increase the risk of diabetes mellitus, *N* (%)[a]			
Never used	1,110,726 (83.05)	1,014,621 (83.15)	96,105 (81.94)
Past use	184,404 (13.79)	167,650 (13.74)	16,754 (14.29)
Using for <90 days	15,189 (1.14)	13,749 (1.13)	1440 (1.23)
Using for ≥90 days	27,133 (2.03)	24,151 (1.98)	2982 (2.54)
Years of follow-up, (IQR)	4.93 (4.93–4.93)	4.93 (4.93–4.93)	4.93 (3.12–4.93)
Years until incident diabetes, (IQR)[b]	2.16 (1.03–3.41)	2.19 (1.05–3.42)	1.90 (0.88–3.18)
Outpatient serum creatinine measurements during follow-up, *N* (IQR)	7 (4–10)	7 (4–10)	6 (3–10)
Outpatient BUN measurements during follow-up, *N* (IQR)	7 (4–11)	7 (4–11)	6 (3–11)
Albuminuria measurements during follow-up, *N* (IQR)	2 (1–4)	2 (1–5)	2 (1–5)
HbA1c measurements during follow-up, *N* (IQR)	2 (1–3)	2 (1–3)	1 (0–3)
Incident diabetes mellitus, *N* (%)	172,913 (12.93)	159,235 (13.05)	13,678 (11.66)
Competing risk, *N* (%)[c]	210,278 (15.72)	168,062 (13.77)	42,216 (36.00)
Weighted incident diabetes mellitus, *N* (%)[d]	210,872.51 (15.73)	187,223.52 (15.32)	23,649.00 (19.85)

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a]Grouped into 4 levels as never used, did not use before T_0, past use, not using at T_0 but used before T_0; using <90 days: using and the newest prescription starts within 90 days before T_0; using ≥90 days: using and the newest prescription starts more than 90 days before T_0.
[b]In participants who experienced incident diabetes.
[c]Competing risk included death, kidney transplantation, and dialysis.
[d]Based on pseudo cohort by inverse probability weighting. Pseudo cohort with population of 1,340,997.99; 1,221,858.67 with BUN ≤25 mg/dl, and 119,139.32 with BUN >25 mg/dl.

of age) (HR, 1.35; 95% CI 1.33–1.37) than those who were older than 65.1 years of age (HR, 1.20; 95% CI 1.16–1.24). Race also modified the association of BUN and the risk of incident diabetes mellitus (*P* value for interaction <0.001); BUN >25 mg/dl was more strongly associated with an increased risk of diabetes among blacks (HR, 1.38; 95% CI

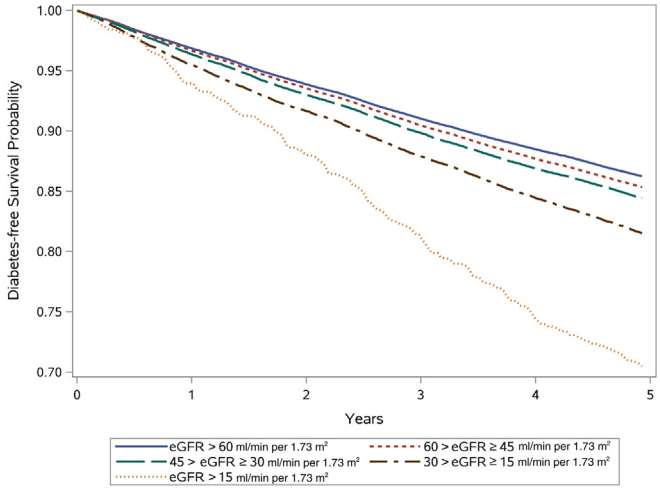

Figure 1 | Diabetes-free survival curves by time-updated estimated glomerular filtration rate (eGFR) categories (eGFR in ml/min per 1.73 m^2).

1.34–1.43) and those of other races (HR, 1.31; 95% CI 1.26–1.38) than whites (HR, 1.21; 95% CI 1.20–1.22).

Association between baseline (T_0) BUN and the risk of incident diabetes

We repeated the primary analyses in models in which we considered baseline BUN (at T_0) as the primary predictor. However, individuals with a high BUN level have a significantly increased risk of ESRD and early death and thus have a much higher probability of experiencing a competing risk than cohort participants with a BUN level ≤25 mg/dl. We therefore used an inverse probability weighting approach to address this bias. The 5-year diabetes-free survival probability by BUN at T_0 is depicted in Figure 6. In a joint risk model (of eGFR and BUN), the risk of incident diabetes was significantly increased at all eGFR levels in those with a BUN level >25 mg/dl (Table 4). A spline analysis of the relationship between BUN level and the risk of incident diabetes showed that the risk of incident diabetes was progressively higher as BUN increased (Figure 7). In models in which eGFR was included as a continuous covariate, compared with a BUN level ≤25 mg/dl, a BUN level >25 mg/dl was associated with an increased risk of incident diabetes mellitus (HR, 1.18; 95% CI 1.15–1.20). In the same model, every 10 ml/min per 1.73 m^2 increase in eGFR was not associated with the risk of incident diabetes mellitus (HR, 1.00; 95% CI 0.99–1.00). In 2-step residual inclusion models, every 10-mg/dl increase in BUN concentration was associated with a significant increase in the risk of incident diabetes mellitus (HR, 1.09; 95% CI 1.08–1.10), whereas every 10 ml/min per 1.73 m^2 increase in eGFR yielded no significant change in the risk of diabetes

Table 2 | Association between time-updated eGFR and risk of incident diabetes mellitus

eGFR category	Total person-years	Incidence rate (95% CI)	HR (95% CI)
eGFR ≥60 ml/min per 1.73 m^2	4,452,049.12	2.99 (2.98–3.01)	1.00
60 > eGFR ≥45 ml/min per 1.73 m^2	797,197.65	3.20 (3.16–3.24)	1.04 (1.03–1.06)
45 > eGFR ≥30 ml/min per 1.73 m^2	293,385.30	3.42 (3.36–3.49)	1.08 (1.06–1.10)
30 > eGFR ≥15 ml/min per 1.73 m^2	62,041.83	4.13 (3.97–4.29)	1.17 (1.12–1.22)
eGFR <15 ml/min per 1.73 m^2	5128.49	7.03 (6.33–7.80)	1.64 (1.48–1.82)

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio. Incident rate per 100 person-years.
The primary predictor was time-varying eGFR category and eGFR ≥60 ml/min per 1.73 m^2 served as the reference category.
Survival model controlled for time-independent variables including age, race, and sex and time-varying variables including carbon dioxide, body mass index, albuminuria, frequency of outpatient encounters, frequency of hospitalizations, chronic lung disease, peripheral artery disease, cardiovascular disease, cerebrovascular disease, dementia, hyperlipidemia, hepatitis C, HIV, cancer, and use of medications that increase the risk of diabetes mellitus.

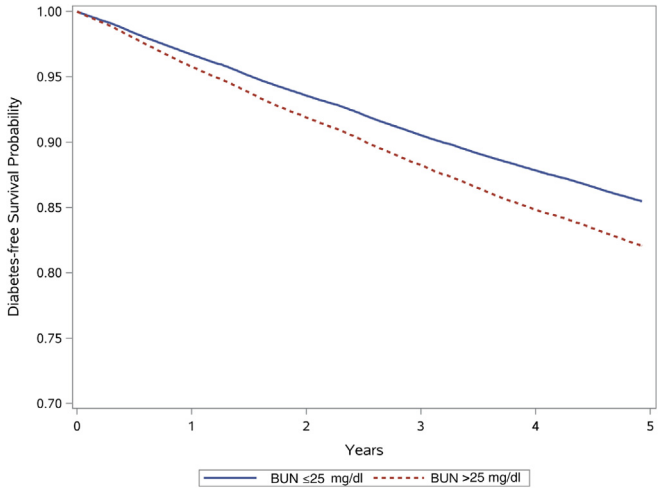

Figure 2 | Diabetes-free survival curves by time-updated blood urea nitrogen (BUN) categories; BUN in mg/dl.

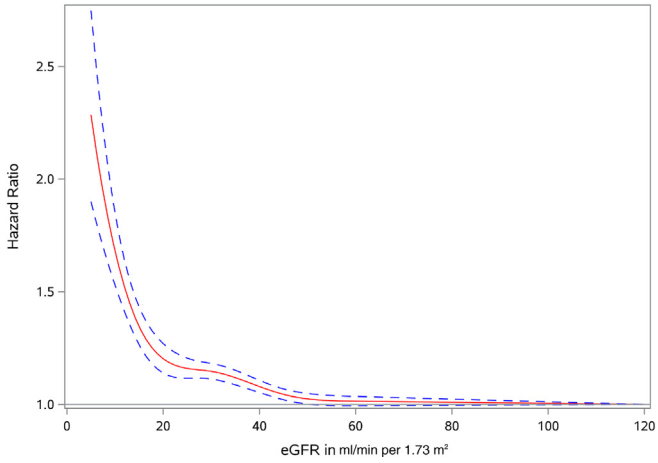

Figure 3 | Spline analysis of the relationship between time-updated estimated glomerular filtration rate (eGFR) and risk of incident diabetes mellitus. The red line represents the hazard ratio, and dashed blue lines represent 95% confidence intervals. eGFR = 120 ml/min per 1.73 m^2 was the reference.

Table 3 | Joint risk model of the risk of incident diabetes mellitus by time-updated BUN and eGFR category

	BUN ≤25 mg/dl			BUN >25 mg/dl		
eGFR category	Total person-years	Incidence rate (95% CI)	HR (95% CI)	Total person-years	Incidence rate (95% CI)	HR (95% CI)
eGFR ≥60 ml/min per 1.73 m^2	4,323,029.13	2.97 (2.95–2.99)	1.00	129,019.99	3.80 (3.69–3.90)	1.27 (1.24–1.31)
60 > eGFR ≥45 ml/min per 1.73 m^2	643,468.56	3.08 (3.04–3.13)	1.02 (1.00–1.03)	153,729.09	3.71 (3.62–3.81)	1.23 (1.20–1.27)
45 > eGFR ≥ 30 ml/min per 1.73 m^2	134,845.64	3.15 (3.06–3.25)	1.00 (0.97–1.03)	158,539.66	3.65 (3.56–3.75)	1.18 (1.15–1.22)
30 > eGFR ≥ 15 ml/min per 1.73 m^2	7420.53	3.51 (3.10–3.96)	0.97 (0.86–1.10)	54,621.30	4.22 (4.05–4.39)	1.22 (1.17–1.27)
eGFR <15 ml/min per 1.73 m^2	251.12	5.16 (2.74–8.82)	1.43 (0.83–2.47)	4877.37	7.13 (6.40–7.92)	1.68 (1.51–1.87)

CI, confidence interval; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
Incident rate per 100 person-years.
The primary predictor was the time-varying combination of BUN and eGFR categories. BUN ≤25 mg/dl and eGFR ≥60 ml/min per 1.73 m^2 served as the reference category. Survival model controlled for time-independent variables age, race, and sex and time-varying variables carbon dioxide, body mass index, albuminuria, frequency of outpatient encounters, frequency of hospitalizations, chronic lung disease, peripheral artery disease, cardiovascular disease, cerebrovascular disease, dementia, hyperlipidemia, hepatitis C, HIV, cancer, and use of medications that increase the risk of diabetes mellitus.

mellitus (HR, 0.99; 95% CI 0.99–1.00). Analyses in which we excluded cohort participants who experienced kidney transplantation, dialysis, or death during follow-up yielded consistent results.

Sensitivity analyses

In order to test the robustness of our study results to changes in epidemiologic design and statistical specifications, we performed the following sensitivity analyses. All sensitivity analyses were undertaken using time-updated models. We considered, in a joint risk model, the association between BMI and eGFR category and the risk of incident diabetes. The results suggest that in those who were underweight, of normal weight, or overweight, as the eGFR decreased, the risk of incident diabetes increased significantly (Supplementary Table S3, Supplementary Figure S1). In cohort participants with obesity (BMI ≥30 kg/m^2), the risk of diabetes was uniformly elevated in all eGFR categories. We then considered the joint association of BMI and BUN level (categorized as >25 or ≤25 mg/dl and separately in quintiles) with the risk of incident diabetes. As the BUN level increased, the risk of incident diabetes increased in the following BMI categories: underweight, normal, and overweight. The risk was uniformly increased in those with obesity (BMI ≥30 kg/m^2) (Supplementary Tables S4 and S5 and Supplementary Figures S2 and S3). Because gastrointestinal bleeding may lead to an increased BUN level, we repeated the analyses in which we considered gastrointestinal conditions associated with bleeding as covariates; the results were consistent (Supplementary Table S6). Exposure to corticosteroids may also elevate BUN levels and increases the risk of diabetes mellitus. Including exposure to corticosteroids as a covariate

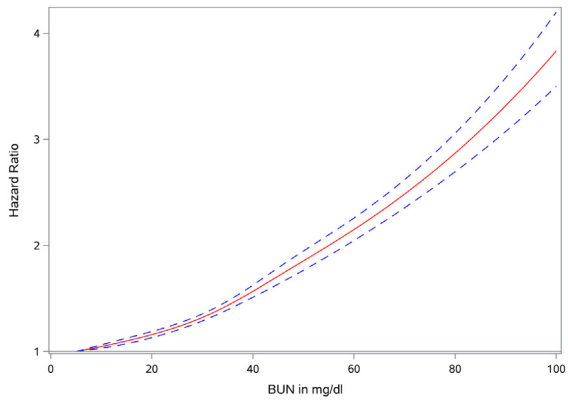

Figure 4 | Spline analysis of the relationship between time-updated blood urea nitrogen (BUN) and risk of incident diabetes mellitus. The red line represents the hazard ratio, and dashed blue lines represent 95% confidence intervals. BUN = 5 mg/dl was the reference.

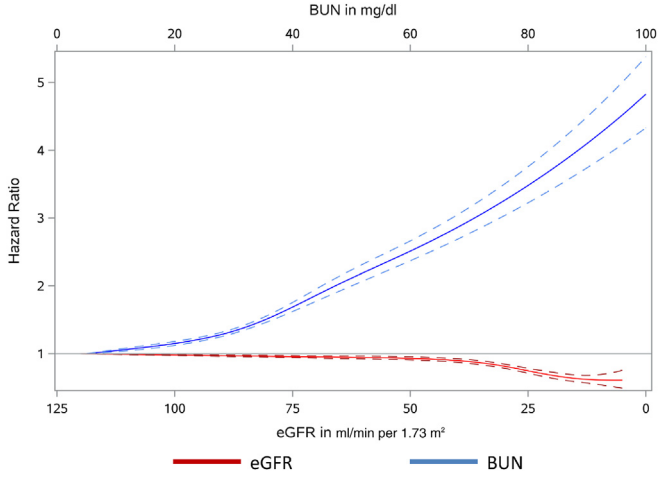

Figure 5 | Spline analysis of risk of incident diabetes mellitus including both time-updated estimated glomerular filtration rate (eGFR) and blood urea nitrogen (BUN). eGFR = 120 ml/min per 1.73 m^2 and BUN = 5 mg/dl were the reference points.

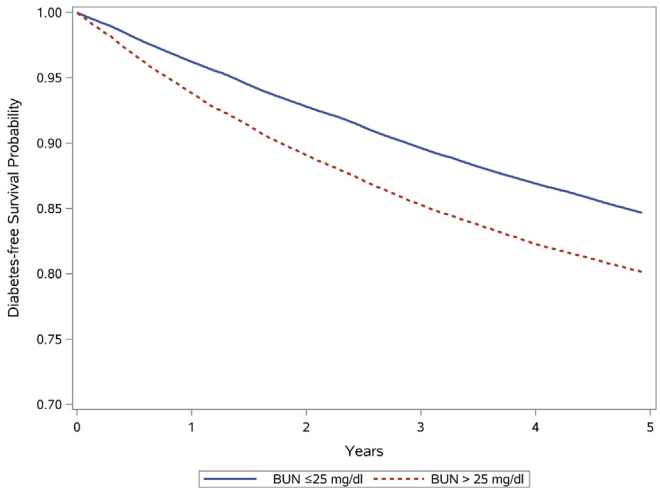

Figure 6 | Diabetes-free survival curves by baseline blood urea nitrogen (BUN) categories; BUN in mg/dl.

in the models yielded results consistent with those shown in the primary analyses (Supplementary Table S7). We repeated the analyses using the MDRD (Modification of Diet in Renal Disease) study equation to compute the eGFR, and the results were consistent (Supplementary Table S8). Because the presence of albuminuria may in some instances triggers the discovery of underlying diabetes (where it was long present but undiagnosed), we repeated the analyses excluding all participants with albuminuria during follow-up; the results were consistent with those shown in primary analyses (Supplementary Table S9). Because the existence of albuminuria at cohort entry (T_0) may be caused by existing diabetes that has not yet been diagnosed and documented, we repeated the entire cohort building process in which we excluded those with any albuminuria within 5 years before T_0 from cohort entry; the analyses yielded findings consistent with the primary results (Supplementary Table S10). Because the diagnosis of diabetic retinopathy in a newly diagnosed individual with diabetes likely suggests that diabetes was present (but undiagnosed for a prolonged period of time), we also considered analyses in which we excluded participants with diabetic retinopathy during follow-up, and the results were consistent (Supplementary Table S11). Analyses in which we excluded secondary diabetes during follow-up also yielded consistent results (Supplementary Table S12). Because the frequency of eGFR and BUN measurements may bias the results, we conducted analyses in which we additionally controlled for the number of eGFR and BUN measurements, and the results were consistent (Supplementary Table S13).

Because baseline HbA_{1c} may influence the future risk of diabetes and may potentially confound a putative independent relationship between the BUN level and the risk of diabetes, we controlled for baseline HbA1c in a subcohort of participants with available baseline HbA1c data ($N = 677{,}234$); a BUN level >25 mg/dl was associated with an increased risk of diabetes defined by diagnostic codes or the use of diabetic medications (HR, 1.18; 95% CI 1.15–1.21)

Table 4 | Joint risk model of the risk of incident diabetes mellitus by baseline BUN and eGFR category

	BUN ≤25 mg/dl				BUN >25 mg/dl			
eGFR category	Weighted no. of participants	Weighted event rate (%)	Weighted incidence rate (95% CI)	HR (95% CI)	Weighted no. of participants	Weighted event rate (%)	Weighted incidence rate (95% CI)	HR (95% CI)
eGFR ≥60 ml/min per 1.73 m^2	1,023,635.80	154,043 (15.05)	3.32 (3.31–3.34)	1.00	27,994.12	4638.24 (16.57)	3.71 (3.60–3.82)	1.06 (1.02–1.10)
60 > eGFR ≥ 45 ml/min per 1.73 m^2	162,930.22	26,453.10 (16.24)	3.62 (3.58–3.66)	0.99 (0.97–1.01)	36,621.67	6838.55 (18.67)	4.25 (4.15–4.35)	1.13 (1.09–1.17)
45 > eGFR ≥ 30 ml/min per 1.73 m^2	33,316.35	6101.78 (18.31)	4.17 (4.06–4.27)	1.05 (1.01–1.09)	39,564.70	8293.58 (20.96)	4.87 (4.76–4.97)	1.21 (1.16–1.26)
30 > eGFR ≥ 15 ml/min per 1.73 m^2	1821.51	383.69 (21.06)	4.88 (4.41–5.40)	1.12 (0.94–1.33)	15,335.59	4461.49 (29.09)	7.27 (7.06–7.49)	1.63 (1.50–1.78)
eGFR <15 ml/min per 1.73 m^2	38.95	10.21 (26.22)	6.50 (3.14–11.89)	1.49 (0.41–5.38)	2803.75	1044.47 (37.25)	10.34 (9.72–10.99)	2.07 (1.19–3.59)

BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
Incident rate per 100 person-years.
The primary predictor was a combination of baseline BUN and eGFR categories. BUN ≤25 mg/dl and eGFR ≥60 ml/min per 1.73 m^2 served as the reference category.
Survival model controlled for baseline age, race and sex, carbon dioxide, body mass index, albuminuria, frequency of outpatient encounters, frequency of hospitalizations, chronic lung disease, peripheral artery disease, cardiovascular disease, cerebrovascular disease, dementia, hyperlipidemia, hepatitis C, HIV, cancer, and the use of medications that increase the risk of diabetes mellitus.

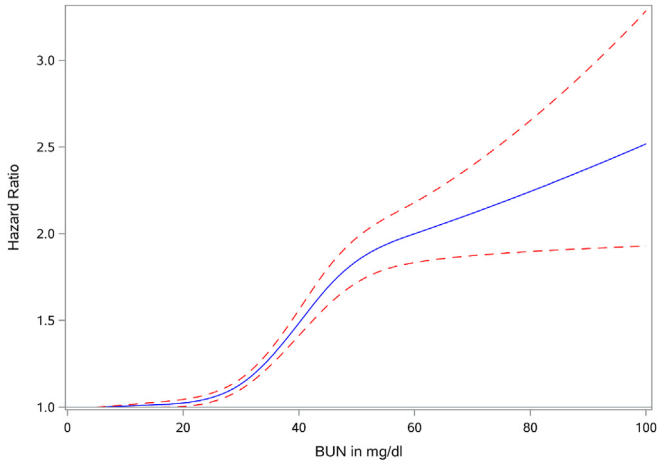

Figure 7 | Spline analysis of the relationship between baseline blood urea nitrogen (BUN) and risk of incident diabetes mellitus. The red line represents the hazard ratio, and dashed blue lines represent 95% confidence intervals. BUN = 5 mg/dl was the reference.

and an increased risk of diabetes defined by diagnostic codes, use of diabetic medications, or HbA1c >6.4 (HR, 1.24; 95% CI 1.21–1.27).

Because the frequency of HbA1c testing may bias the results, we (i) used the overall cohort and included the time-updated number of HbA1C measurements as a covariate; a BUN level >25 mg/dl was associated with an increased risk of diabetes (HR, 1.22; 95% CI 1.20-1.24); and (ii) restricted the analyses to a subcohort of those with at least 1 HbA1c measurement (N = 677,234) while also controlling for the number of HbA1C measurements; a BUN level >25 mg/dl was associated with an increased risk of diabetes (HR, 1.22; 95% CI 1.20–1.25).

We examined the relationship between BUN and the risk of each component of the composite outcome separately; BUN level>25 mg/dl was associated with an increased risk of diabetes defined by diagnostic codes (HR, 1.18; 95% CI 1.16–1.21), use of diabetic medications (HR, 1.13; 95% CI 1.09–1.17), and HbA1c >6.4 (HR, 1.25; 95% CI 1.22–1.28).

Finally, we considered eGFR and BUN on the $\log_{10}$ scale; a per-unit increase in $\log_{10}$ eGFR was associated with a decreased risk of incident diabetes (HR, 0.80; 95% CI 0.77–0.83) (Supplementary Figure S4); a per-unit increase in $\log_{10}$ BUN level was associated with an increased risk of incident diabetes (HR, 1.56; 95% CI 1.51–1.61) (Supplementary Figure S5). Spline analyses in which both $\log_{10}$ eGFR and $\log_{10}$ BUN level were included suggested that whereas the risk of incident diabetes mellitus increased with increased BUN concentrations, the risk was decreased with a decreased eGFR (Supplementary Figure S6).

DISCUSSION

Using a big data approach, we examined the association between BUN and the risk of incident diabetes in a cohort of 1,337,452 US veterans followed for a median of 4.93 years (5,609,802.38 person-years). Our findings show that as the eGFR decreased and the BUN level increased, the risk of incident diabetes became progressively more pronounced. Results from joint risk models of eGFR and BUN (in which BUN was considered as >25 mg/dl and ≤25 mg/dl and separately in quintiles), spline analyses, which allow for the examination of the association of BUN and risk of incident diabetes in a nonlinear form while considering BUN as a continuous variable,[11] analyses that included both eGFR and BUN concurrently and 2-step residual inclusion models (which allow examination of the impact of BUN independent of its correlation with the eGFR) support the conclusion that a higher concentration of BUN is associated with an increased risk of incident diabetes mellitus. The results were robust to challenges in multiple sensitivity analyses.

The kidney is an important organ in glucose homeostasis,[7,12] which relies on the adequate production of insulin from pancreatic beta cells and adequate action of insulin in peripheral tissues.[6] Both production of insulin and tissue sensitivity to insulin are impaired in the setting of CKD.[1,13,14] The mechanisms underlying the disturbances of glucose homeostasis are becoming clearer and likely involve retention of uremic metabolites including urea, and p-cresyl sulfates, modification of gut microbiome, oxidative stress, and inflammation. Other conditions including metabolic acidosis, aging, and excess angiotensin II may result in insulin resistance.[1,8,14] Earlier observations by Pham *et al.*[2] and de Boer *et al*[4] clearly demonstrated that kidney disease results in a state of increased insulin resistance (and reduced insulin sensitivity). In an elegant body of work, Koppe *et al.*[13] demonstrated that retention of renally excreted compounds including p-cresyl sulfate mechanistically contributes to the genesis of the state of insulin resistance in the setting of kidney disease. D'Apolito *et al.*[5] reported that urea caused increased reactive oxygen species production, increased insulin resistance, and glucose intolerance in uremic mice and that treatment with a superoxide dismutase/catalase mimetic normalized these defects. This treatment also abrogated the development of insulin resistance in normal mice following infusion of urea.[5] In recent seminal observations, Koppe *et al.*[6] further demonstrated that beta-cell dysfunction is an important contributor to deranged glucose homeostasis in experimental CKD and that kidney disease is associated with defective insulin secretion and that insulin secretory defects in CKD are mechanistically linked to elevated levels of the major uremic metabolite urea. A few small studies reported a relationship between low eGFR and elevated levels of cystatin C and the odds of diabetes mellitus.[15,16]

Our results provide epidemiologic evidence to support those mechanistic studies by D'Apolito *et al.*[5] and Koppe *et al.*[6] in that we found that risk of diabetes is increased in those with a higher BUN level (>25 mg/dl) regardless of eGFR levels (and that the relationship between the eGFR and the risk of diabetes was nonsignificant in those with a BUN level ≤25 mg/dl); the risk relationship (between the BUN level and the risk of diabetes) appears exponential in nature in that risk progressively increased with increased BUN levels.

Furthermore, our 2-stage residual inclusion analyses (which account for the intimate correlation between eGFR and BUN) suggest that the significant increase in the risk of diabetes as the eGFR decreased is most likely due to its correlation with the BUN level. Spline analyses that included both the eGFR and BUN level showed that the risk of diabetes was increased with an increased BUN level and the risk was decreased with a decreased eGFR; therefore, endorsing the finding that the risk of diabetes seen with a low eGFR is most likely accounted for by a high BUN level in that context. Taken together, the constellation of findings suggests that in advanced kidney disease and consistent with the experimental evidence, an elevated BUN level is associated with an increased risk of incident diabetes mellitus.

Although increased insulin resistance in CKD is now a universally recognized concept, the notion of beta-cell dysfunction (and possibly an insulin secretory defect) in CKD is still not yet widely accepted.[1,6,13,17] That our study results are congruent with the experimental observations of Koppe *et al.*[1,6] and D'Apolito *et al.*[5] lends validity and provides epidemiologic evidence in humans of an association between circulating levels of urea and the risk of the development of diabetes in patients with nondiabetic kidney disease. However, our studies cannot attribute the effect seen to decreased insulin secretion (and beta-cell dysfunction) or increased insulin resistance or a combination of both. Further studies are required to validate these findings in other cohorts and to examine whether interventions (by pharmacologic means, microbiome manipulation, or other methods) to reduce urea or its downstream effects will result in a decreased risk of diabetes mellitus.

Because obesity is an important driver of both kidney disease and diabetes, we evaluated the risk of diabetes in joint risk models of eGFR and BMI and separately of BUN and BMI, the results show that as kidney function deteriorates, the risk of diabetes increases in all BMI categories except for those with obesity, most likely owing to the profoundly increased risk of diabetes in that setting, which may have dwarfed a relatively less strong risk factor (decreased eGFR and elevated BUN level).[18,19]

Although experimental evidence identifies urea as a putative culprit and although our epidemiologic human observations suggest an association between the BUN level and the risk of diabetes, it is important to note that our studies focused on urea; however, in the setting of CKD, a significant number of metabolites including indoxyl sulfate, p-cresyl sulfate, and numerous others are increased, and they may either have contributed to or were responsible for the association described in this report.[20] The furan fatty acid metabolite 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, at concentrations found in CKD patients, also impairs insulin secretion via a mechanism involving mitochondrial dysfunction and abrogation of insulin biosynthesis in beta cells.[21] Furthermore, metabolic derangements associated with CKD including metabolic acidosis, dyslipidemia, hyperuricemia, hypovitaminosis D, disordered bone and mineral metabolism, and, in particular, secondary hyperparathyroidism may result in beta-cell dysregulation.[1,6,21–26]

Our study has a number of limitations. The analytic cohort included mostly older white male US veterans, which may limit the generalizability of study results. Although we accounted for known confounders, we cannot exclude the possibility of residual confounders (either unmeasured or unknown). de Boer *et al.*[4] described reduced insulin sensitivity and clearance that are, in part, explained by differences in lifestyle and body composition; our databases did not include information on these parameters. A low-protein diet ameliorates insulin sensitivity[27]; although we included serum bicarbonate, a surrogate marker of protein intake, as a covariate in the models, our datasets did not include information on dietary intake. Because declining kidney function may lead to increased health care use, it is likely that this increased intensity of care may have resulted in the identification of diabetes and hence explains the risk seen in this report (Berksonian bias).[28,29] We have, however, taken care to include measures of health care use and intensity of care as covariates in the models. In addition, we have considered analyses in which we excluded participants in whom albuminuria developed before cohort entry (as it might be caused by diabetes that has not been yet diagnosed) or during the time in cohort (as it is likely to trigger the discovery of otherwise occult diabetes) and diabetic retinopathy (which is likely indicates that diabetes was present for a long time but was not diagnosed) during the time in the cohort, and the results remained robust. In addition, given the correlated relationship between eGFR and BUN level, we developed analytic strategies to disentangle the effects of eGFR and BUN for which we built joint risk models and used 2-step residual estimation methods to evaluate the independent impact of BUN on the risk of incident diabetes.[10] The study has a number of strengths including the use of national large-scale data from a network of integrated health systems that were captured during routine medical care, which minimizes selection bias. In sum, our results show an association between higher levels of BUN and the risk of incident diabetes mellitus. A nexus (and, more specifically, a bidirectional relationship) likely exists between diabetes mellitus and kidney disease in that diabetes is (indisputably) a driver of kidney disease, and emerging evidence suggests that urea (and possibly other uremic components) may increase the risk of diabetes. Future research should examine whether higher levels of urea are associated with poorer diabetes control and poorer outcomes among diabetic patients and whether elevated levels of urea are associated with an increased risk of failure of oral hypoglycemic agents and increased need for insulin.

MATERIALS AND METHODS

Cohort participants

Using the US Department of Veterans Affairs administrative database, we selected 4,605,535 participants enrolled in the VA Health Care System before October 1, 2003. We then excluded those without an outpatient serum creatinine measurement between October 1, 2007 and October 1, 2008 (2,199,385 participants); for those with a measurement in this period, we designated the date of last eGFR measurement as T_0. We then additionally excluded those with diabetes mellitus before T_0 (906,523 participants) (where washout period spanned at least 5 years [October 1, 2003–October 1, 2008] or longer for those enrolled in the US Department of Veterans Affairs health care system before October 1, 2003), yielding an intermediate cohort of 1,499,627 participants. We further removed those with missing data on weight, height, BUN level, and serum carbon dioxide before T_0 (157,140 participants) and those who underwent dialysis or kidney transplantation before T_0 (5035 participants), yielding the final analytic cohort of 1,337,452 participants (Figure 8). The study was approved by the Institutional Review Board of the VA St. Louis Health Care System, St. Louis, MO.

Data sources

Veterans Health Administration Medical SAS Inpatient and Outpatient Datasets that contain national Veterans Health Administration health care encounters data were used to collect information on International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic codes.[30] The Veterans Health Administration's Managerial Cost Accounting System and Corporate Data Warehouse Lab Chemistry domain provided laboratory results information.[18,19,31–33] The VA Corporate Data Warehouse Outpatient Pharmacy domain provided information on outpatient prescriptions.[28,29,33] The Vital Signs domain provided information on height and weight to compute BMI. The VA Beneficiary Identification Records Locator Subsystem files, Medical SAS, and Vital Status datasets provided demographic characteristics.[30] Information about occurrence of dialysis and kidney transplantation was obtained from the United States Renal Database System.[34]

Primary predictor variables

The primary predictor variables were time-varying outpatient eGFR and outpatient BUN level. Because the eGFR and BUN level were not measured at every time point, the values were imputed by the measurements before and closest to the time point when no measurements were taken. The eGFR and BUN level measurements were carried forward 154.89 days (interquartile range, 102.65–252.68) and 150.24 days (interquartile range, 100.57–231.78), respectively. The eGFR was computed based on the Chronic Kidney Disease Epidemiology Collaboration equation and was classified into 5 categories: eGFR $\geq$60 ml/min per 1.73 m^2, 60 $>$ eGFR $\geq$ 45 ml/min per 1.73 m^2, 45 $>$ eGFR $\geq$ 30 ml/min per 1.73 m^2, 30 $>$ eGFR $\geq$ 15 ml/min per 1.73 m^2, and, eGFR$<$15 ml/min per 1.73 m^2 with no kidney transplant or dialysis. BUN levels were classified as high (BUN $>$25 mg/dl) and low (BUN $\leq$25 mg/dl) categories and as quintiles based on the ranking at each time point.

Outcome

The outcome of this study was incident diabetes mellitus. Diabetes mellitus was defined as any occurrence of the following: International Classification of Diseases 9 codes 250.X, 357.2, 362.0, and 366.41; diabetes medication prescription (including insulins and oral hypoglycemic agents); or an HbA1c test result $>$6.4%.[35]

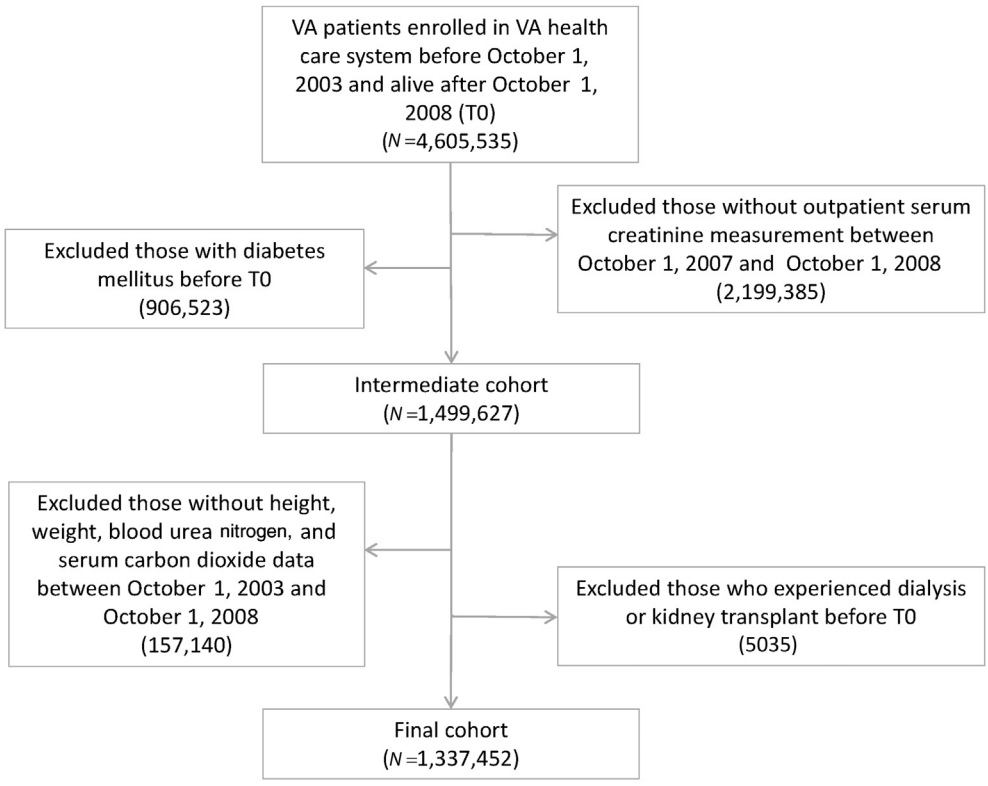

Figure 8 | Flowchart of cohort assembly. VA, Veterans Affairs.

Covariates

Covariate curation was informed by previous evidence.[28,29,36–38] Covariates were measured from 5 years before T_0 until the end of follow-up. Comorbidities included cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, dementia, cancer, hypertension, hyperlipidemia, hepatitis C, and HIV. All comorbidities were assigned based on relevant International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic codes except for hepatitis C and HIV, which were assigned based on laboratory results.[28,29,36–40] Comorbidities were time varying and considered to exist until the end of follow-up once diagnosed. BMI was categorized into underweight (BMI <18.5 kg/m^2), normal (18.5 kg/m^2 $\leq$ BMI <25 kg/m^2), overweight (25 kg/m^2 $\leq$ BMI <30 kg/m^2), and obese (30 kg/m^2 $\leq$ BMI). Albuminuria status was a dichotomous variable for which a microalbumin/creatinine ratio >30 mg/g was considered albuminuria. Serum carbon dioxide was treated as a continuous variable. BMI, albuminuria, and serum carbon dioxide at time t were considered to have the same value as the measurement at or before and closest to time t. The number of hospitalizations and outpatient encounters were accumulated from 5 years before T_0 and grouped into 4 groups based on ranking at each time point. Based on the number, frequency of hospitalizations was then classified into never hospitalized or split into tertiles (low, medium, and high), whereas frequency of outpatient encounters was grouped into quartiles. Information about medications that increase the risk of diabetes mellitus (including corticosteroids, tacrolimus, cyclosporine, pentamidine, nicotinic acid, and some antiretrovirals) were used to create a 4-level time-varying variable at time t, where users were categorized as never use when there was no record of medication use between October 1, 2003 and time t, past use when the last record of medication was between October 1, 2003 and time t; current use <90 days when the last record of medication is at time t but does not extend 90 days before time t; and current use 90 days or greater when the prescription is current at time t and extends $\geq$90 days before time t. Besides time-varying variables, time-independent variables including age; race defined as white, black and other; and sex were also included in multivariate analyses as covariates. Participants with missing baseline covariates were excluded from study entry. A value carry forward approach was applied to the data missing during follow-up.

Statistical analyses

Means and SDs, counts and percentages, and medians and interquartile ranges were used to describe cohort characteristics at T_0. The Simon and Makuch method for diabetes-free survival curves, which evaluates a participant's exposure status at each event time and takes into account the change in exposure status over time, was used for time-dependent eGFR categories and BUN categories.[41] Kaplan-Meier curves were used to depict diabetes-free survival probability by baseline BUN categories.

Assuming a nearly contemporaneous relationship between exposure and outcome, time-varying multivariate Cox survival models, which included a time-varying primary predictor and covariates, were used to examine the relationship between the predictor and risk of incident diabetes mellitus. Because time-varying analyses with large datasets are computationally demanding, the time unit of analyses was set at 10 days. Multiple approaches were applied to evaluate the relationship between BUN level and diabetes mellitus while accounting for eGFR: we built joint risk models in which the predictor was categorized based on BUN and eGFR categories; we controlled for eGFR as a continuous variable in order to account for possible reverse causation; we applied a 2-stage residual inclusion method to examine the effect of BUN uncorrelated with eGFR.[10] The residual inclusion method involved 2 regressions. In the first stage, BUN level at each time point was regressed on the log of eGFR to yield a residual. In the second stage, the residuals, as time varying, were used in place of BUN as the primary predictor in a Cox survival model while controlling for covariates and the log of eGFR. All models controlled for age, race, sex, chronic lung disease, peripheral artery disease, cardiovascular disease, cerebrovascular disease, dementia, hyperlipidemia, hepatitis C, HIV, cancer, BMI, serum carbon dioxide, frequency of hospitalization, frequency of outpatient encounters, albuminuria, and use of medications that increase the risk of diabetes mellitus. Death and end-stage renal disease (ESRD) during follow-up were considered competing risks; therefore, in all analyses, we used competing risk models to estimate the cause-specific hazards.[42–45] Cubic spline regressions were used to examine the nonlinear relationship between the predictor and outcomes,[46] where eGFR was restricted to between 5 and 120 ml/min per 1.73 m^2 and the BUN level was restricted to between 5 and 100 mg/dl to avoid the influence of extreme values.

In addition, we also examined the association between baseline exposure and outcome. This analytic strategy is guided by the notion that exposure to higher levels of BUN must occur for a sufficient duration of time to eventually result in reduced insulin sensitivity and reduced insulin secretion and subsequently manifest in clinically diagnosable diabetes (the outcome in this study). The probability of experiencing competing risk (of ESRD and death) was significantly higher among those with a high BUN level. We therefore applied an inverse probability weighting approach to resample a pseudo population from cohort.[47,48] In detail, each cohort participant's probability of not experiencing competing risk during follow-up given baseline variables was calculated from logistic regression. Then those who did not experience competing risk were weighted by the inverse of the probability to create the pseudo population. Analyses were done within the pseudo population to examine the association between baseline exposure (BUN at T_0) and outcome given baseline covariates in the situation that no competing risk occurs. We also built analyses to examine the association in a cohort where we excluded those with a competing risk.

In analyses, a 95% CI that does not include 1.00 was considered statistically significant. All analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC).

Sensitivity analyses

To evaluate the association between the predictor and risk of diabetes mellitus in different settings, we conducted multiple sensitivity analyses. (i) We built a joint risk model to evaluate the effect of eGFR and BMI categories on developing diabetes. (ii) We built a joint risk model to evaluate the association of BUN level and BMI categories with diabetes. (iii) We additionally controlled for gastrointestinal bleeding, which would affect BUN levels. (iv) We additionally controlled for steroids, which may also affect BUN levels and increase the risk of diabetes. In this analysis, we did not control for other medications that increase the risk of diabetes mellitus to avoid collinearity. (v) We repeated the analyses using the MDRD (Modification of Diet in Renal Disease) Study equation to calculate eGFR. (vi) We excluded participants with albuminuria during the follow-up to modify the outcome definition as diabetes

mellitus without albuminuria. (vii) We excluded those who experienced albuminuria within 5 years before T_0 because such albuminuria may have been caused by existing diabetes that has not yet been diagnosed and documented. (viii) We excluded participants with diabetic retinopathy during follow-up. (ix) We excluded participants diagnosed with secondary diabetes mellitus during follow-up. (x) To account for the potential confounding related to the frequency of eGFR and BUN measurements, we additionally controlled for the number of eGFR and BUN measurements during follow-up. (xi) We controlled for baseline HbA1c within those with available baseline HbA1c data. (xii) To account for potential bias introduced by the frequency of HbA1c measurements, we controlled for the time-updated number of HbA1c measurements and examined the association in those with at least 1 HbA1c measurement. (xiii) We examined the relationship between BUN level and risk of each component of the composite outcome separately. (xiv) We also considered analyses in which eGFR and BUN were $\log_{10}$ transformed.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Figure S1. Joint risk of incident diabetes mellitus by body mass index and estimated glomerular filtration rate (eGFR) category.
Figure S2. Joint risk of incident diabetes mellitus by body mass index and blood urea nitrogen (BUN) ($\leq$ 25 and $>$25 mg/dl) category.
Figure S3. Joint risk of incident diabetes mellitus by body mass index and blood urea nitrogen (BUN) (in quintiles) category.
Figure S4. Spline analysis of the relationship between time-updated $\log_{10}$ estimated glomerular filtration rate (eGFR) and the risk of incident diabetes mellitus; eGFR = 120 ml/min per 1.73 m^2 ($\log_{10}$ eGFR = 2.08) was the reference.
Figure S5. Spline analysis of the relationship between time-updated $\log_{10}$ blood urea nitrogen (BUN) level and the risk of incident diabetes mellitus. BUN = 5 mg/dl ($\log_{10}$ BUN = 0.70) was the reference.
Figure S6. Spline analysis of risk of incident diabetes mellitus including both time-updated $\log_{10}$ estimated glomerular filtration rate (eGFR) and $\log_{10}$ blood urea nitrogen (BUN). eGFR = 120 ml/min per 1.73 m^2 and BUN = 5 mg/dl were the reference points.
Table S1. Baseline characteristics according to estimated glomerular filtration rate category at time of cohort entry (T_0).
Table S2. Joint model of the risk of incident diabetes mellitus by time-updated BUN categorized in quintiles and estimated glomerular filtration rate categories.
Table S3. Joint risk model of the risk of incident diabetes mellitus by time-updated body mass index and estimated glomerular filtration rate category.
Table S4. Joint risk model of the risk of incident diabetes mellitus by time-updated body mass index and blood urea nitrogen ($>$25 and $\leq$25 mg/dl) category.
Table S5. Joint risk model of the risk of incident diabetes mellitus by time-updated BMI and BUN (in quintiles) category.
Table S6. Joint model of the risk of incident diabetes mellitus by time-updated estimated glomerular filtration rate and blood urea nitrogen category additionally controlled for gastrointestinal bleeding.
Table S7. Joint model of the risk of incident diabetes mellitus by time-updated estimated glomerular filtration rate and blood urea nitrogen category additionally controlled for steroids.
Table S8. Joint model of the risk of incident diabetes mellitus by time-updated estimated glomerular filtration rate and blood urea nitrogen category in which estimated glomerular filtration rate was computed using the MDRD (Modification of Diet in Renal Disease) study equation.
Table S9. Joint model of the risk of incident diabetes mellitus by a time-updated estimated glomerular filtration rate and blood urea nitrogen category from which participants who experienced albuminuria during follow-up were excluded (N = 1,062,505).
Table S10. Joint model of the risk of incident diabetes mellitus by time-updated estimated glomerular filtration rate and blood urea nitrogen category from which participants who experienced albuminuria within 5 years before cohort entry (T_0) were excluded (N = 1,168,611).
Table S11. Joint model of the risk of incident diabetes mellitus by time-updated estimated glomerular filtration rate and blood urea nitrogen category from which participants with diabetic retinopathy during follow-up were excluded (N = 1,330,981).
Table S12. Joint model of the risk of incident diabetes mellitus by time-updated estimated glomerular filtration rate and blood urea nitrogen category from which participants with secondary diabetes mellitus during follow-up were excluded (N = 1,336,422).
Table S13. Joint model of the risk of incident diabetes mellitus by time-updated estimated glomerular filtration rate and blood urea nitrogen category additionally controlled for number of estimated glomerular filtration rate and blood urea nitrogen measurements.
Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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