Metabolites associate with kidney function decline and incident chronic kidney disease in the general population

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ABSTRACT

Background. Serum metabolites are associated cross-sectionally with kidney function in population-based studies.

Methods. Using flow injection and liquid chromatography tandem mass spectrometry methods, we examined longitudinal associations of baseline concentrations of 140 metabolites and their 19 460 ratios with kidney function decline and
chronic kidney disease (CKD) incidence over 7 years in 1104 participants of the Cooperative Health Research in the Region of Augsburg S4/F4 study.

Results. Corrected for multiple testing, a significant association with annual change in the estimated glomerular filtration rate was observed for spermidine (P = 5.8 × 10^{-7}) and two metabolite ratios, the phosphatidylcholine diacyl C42:5-to-phosphatidylcholine acyl-alkyl C36:0 ratio (P = 1.5 × 10^{-6}) and the kynurenine-to-tryptophan ratio (P = 1.9 × 10^{-6}). The kynurenine-to-tryptophan ratio was also associated with significantly higher incidence of CKD at the follow-up visit with an odds ratio of 1.36 per standard deviation increase; 95% confidence interval 1.11–1.66, P = 2.7 × 10^{-5}). In separate analyses, the predictive ability of the metabolites was assessed: both the three significantly associated metabolite (ratios) as well as a panel of 35 metabolites selected from all metabolites in an unbiased fashion provided as much but not significantly more prognostic information than selected clinical predictors as judged by the area under the curve.

Conclusions. Baseline serum concentrations of spermidine and two metabolite ratios were associated with kidney function change over subsequent years in the general population. In separate analyses, baseline serum metabolites were able to predict incident CKD to a similar but not better extent than selected clinical parameters. Our longitudinal findings provide a basis for targeted studies of certain metabolic pathways, e.g. tryptophan metabolism, and their relation to kidney function decline.

INTRODUCTION

Chronic kidney disease (CKD) affects up to 10% of the general population [1]. A decline in kidney function can be accompanied by a change in serum metabolite concentrations [2]. Prior studies showed cross-sectional associations between specific serum metabolite concentrations and their ratios with estimated glomerular filtration rate (eGFR) in the general population [2, 3]. It is unclear whether significant associations between metabolite concentrations and eGFR are a result of reduced kidney function or whether metabolites play an etiologic role in kidney disease development: assessing this relationship over time could provide insights into a possible causal role of specific metabolites in CKD pathogenesis. In this study, we screened for associations between metabolite concentrations measured at baseline and changes in eGFR over subsequent years in the general population. We tested for significant associations between metabolites and the clinically relevant outcome of incident CKD among individuals without CKD at baseline. In addition, we assessed the predictive value of metabolites for incident CKD in comparison to clinical parameters.

MATERIALS AND METHODS

Study design and participants

Participants aged 54–75 years at baseline (S4 visit, 1999–2001) were selected from the KORA (Cooperative Health Research in the Region of Augsburg) study and its first follow-up visit in 2006–08 (F4). Of 3080 individuals who attended both the baseline visit S4 and the follow-up visit F4, 1104 had serum metabolites and covariates measured at the S4 visit and creatinine at both baseline and follow-up visits. Standardized examinations and tests applied to KORA participants have been described in detail [4].

Ethics statement

Written informed consent was obtained from all participants. This study has been approved by the local ethics committee.

Outcome definition

The primary outcome was a change in estimated eGFR. We also evaluated incident CKD at the F4 visit.

The eGFR was calculated from standard creatinine by using the CKD-EPI equation [5].

Annual eGFR change was defined as the difference in eGFR between the KORA S4 and F4 visits divided by the time between visits in years. Creatinine measurements were performed using the enzymatic method at the S4 visit and the Jaffe method at the F4 visit. Creatinine concentrations from both visits were calibrated to representative estimates derived from the Third National Health and Nutrition Examination Survey (NHANES III), using age- and sex-stratified groups as described before [6]. Standard creatinine was calculated for the F4 measurements using the following equation: standard creatinine = 0.95 × calibrated serum creatinine [7]. Enzymatic measurements at S4 did not require standardization.

CKD at baseline was defined as an eGFR <60 mL/min/1.73 m^2 according to the current Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines (n = 87, KORA S4). Incident CKD (n = 106) was defined as an eGFR <60 mL/min/1.73 m^2 at the KORA F4 visit among those with eGFR ≥60 mL/min/1.73 m^2 at the KORA S4 visit. Sensitivity analyses were conducted to additionally evaluate rapid eGFR decline defined as annual eGFR decline >3 mL/min/1.73 m^2.

Metabolomic measurements

KORA S4 serum samples were analysed in 2011 in a single batch. Targeted metabolomic measurements of KORA S4 were based on electrospray ionization flow injection analysis tandem mass spectrometry (ESI-FIA-MS/MS) and electrospray ionization liquid chromatography tandem mass spectrometry (ESI-LC-MS/MS) measurements by the AbsoluteIDQ™ kit p180 (BIOCRATES Life Sciences AG, Innsbruck, Austria). The assay allows simultaneous quantification of 186 metabolites out of 10 μL of serum. The AbsoluteIDQ™ kit p180 is the extended version of the AbsoluteIDQ™ p150 kit and provides quantification of further metabolites by using additional LC-MS/MS separation of the same sample solutions: details of the procedures of the AbsoluteIDQ™ p150 kit and abbreviations used are provided in the references [8–10]. Sample handling was performed by a Hamilton Micro Lab Star robot (Hamilton Bonaduz AG, Bonaduz, Switzerland) and an Ultravap nitrogen evaporator (P vorvair Sciences, Leatherhead, UK). MS analyses were done on an API 4000 QTRAP MS (AB Scien...
Deutschland GmbH, Darmstadt, Germany) coupled to a 1200-Series HPLC (Agilent Technologies Deutschland GmbH, Böblingen, Germany) and a HTC PAL auto sampler (CTC Analytics, Zwingen, Switzerland) controlled by the software Analyst 1.5.1. Measurements were performed as described in the manufacturer manual UM-P180. Analytical specifications for limit of detection (LOD) and evaluated quantification ranges, further LOD for semiquantitative measurements, identities of quantitative and semiquantitative metabolites, specificity, potential interferences, linearity, precision and accuracy, reproducibility and stability were described in BIOCRATES manual AS-P180. The LODs were set to three times the values of the zero samples (phosphate-buffered saline). The lower limit of quantification and the upper limit of quantification were determined experimentally by BIOCRATES. Data evaluation for quantification of metabolite concentrations and quality assessment was performed with the MetIQ™ software package, which is an integral part of the AbsoluteIDQ™ kit p180. Concentrations were calculated with reference to appropriate internal standards as detailed by the manufacturer. The methods of the AbsoluteIDQ™ p180 kit have been proven to be in conformance with the FDA Guideline ‘Guidance for Industry—Bioanalytical Method Validation, May 2001 (US Department of Health and Human Services, Food and Drug Administration (FDA) et al. May 2001), which implies proof of reproducibility within a given error range. Concentrations of the analysed metabolites are reported in μmol/L. All metabolite measurements were performed at the Genome Analysis Centre of the Helmholtz Zentrum München, Germany.

The metabolomics dataset comprised metabolites from various molecular classes; an overview is provided in supplementary material, Table S1. Additional information on metabolomic measurements can be found in the supplemental material.

**Statistical methods**

The statistical analysis plan is outlined in supplementary material, Figure S1. An initial multivariable-adjusted discovery screen was conducted, relating baseline measurements of metabolites and their ratios at the S4 visit with annual changes in eGFR. The metabolites that were significantly associated with subsequent eGFR changes were then related to incident CKD.

Ratios were created pairwise between all of the individual 140 metabolites, yielding a total of 19 460 unique ratios. Serum metabolite levels and their ratios were standardized and analysed per unit change in standard deviation.

Associations of changes in eGFR with metabolites and ratios were obtained from linear regression analyses, adjusted for known CKD risk factors measured at baseline: age (years) [11], gender, body mass index (BMI, kg/m²), systolic blood pressure (mmHg), current smoking status, antihypertensive medication use, antihyperlipidemic medication use excluding herbal medications, serum triglycerides (mg/dL, natural log transformation), serum high-density lipoprotein cholesterol (HDL-C, mg/dL), fasting serum glucose (mg/dL, natural log transformation) and baseline eGFR. Statistical significance was defined as P < 3.6 × 10⁻⁴ (0.05/140) for single metabolites and P < 2.6 × 10⁻⁶ (0.05/19 460) for ratios corresponding to a Bonferroni correction for the number of tested metabolites and ratios. As serum creatinine constitutes an important component of the evaluated outcome, the creatinine measurements performed by MS were excluded from the result tables. For information, we provide the results for creatinine in the text.

Prior studies showed metabolite ratios to sometimes have stronger associations than single metabolites, which may reflect underlying enzymatic processes: therefore, the ‘P-gain’ was computed for all significant ratios from the discovery screen, defined as (minimum [P-numerator, P-denominator])/P-ratio, reflecting the order of magnitude by which the P-value for association of a ratio with annual eGFR change decreased compared with the lower P-value of its individual components [12]. A significant P-gain was defined as being >139 (correction for 140 evaluated metabolites, as done previously) [8].

Significant metabolites and ratios derived from the discovery screen were analysed using multivariable-adjusted logistic regression for association with incident CKD, adjusting for the same covariates as in the initial screening analysis. Additional information about the statistical methods used for the prediction analyses can be found in the supplemental material.

STATA version 11.2, Special Edition (StataCorp LP, College Station, TX) was used for statistical analyses. The screening analyses were verified by a second, independent analyst using R (version 2.11.1; R Foundation for Statistical Computing; www.r-project.org). The correlation matrix was generated using the CIMminer tool (Genomics and Bioinformatics Group, National Cancer Institute, Bethesda, MD).

**RESULTS**

The demographics of the included 1104 participants aged 54–75 years at baseline are shown in Table 1. The mean eGFR was lower at the follow-up F4 visit (2006–08) compared with the baseline S4 visit (1999–2001; median time difference 7.1 years). CKD prevalence increased from 7.9% at baseline to 14.5% at follow-up.

Supplementary material, Figure S2 illustrates the pairwise correlation structure of the metabolites measured at baseline. As expected, the strongest correlations were found within the same molecular classes, e.g. sphingomyelins correlated highly with other sphingomyelins. Creatinine measured as a part of the metabolite panel correlated moderately with other simultaneously measured metabolites; the strongest correlation with creatinine was observed for citrulline (Pearson $r^2 = 0.37$).

Of the measured metabolites, only spermidine was significantly associated with annual decline in eGFR, not considering the metabolomic creatinine measurement (Table 2 and supplementary material, Table S2). Per standard deviation increment in baseline spermidine level, the annual eGFR fell by −0.24 mL/min/1.73 m², $P = 5.8 \times 10^{-7}$ (Table 2). In comparison, the coefficient for creatinine was −0.39 mL/min/1.73 m² ($P = 1.6 \times 10^{-8}$). The screen for annual eGFR decline included 87 individuals with pre-existing CKD (mean baseline
Table 1. Demographic characteristics of the 1104 individuals who participated both in the baseline KORA S4 and the follow-up F4 visit

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>63.3 (5.4)</td>
<td>70.4 (5.4)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>50.9</td>
<td>50.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.4 (4.2)</td>
<td>28.7 (4.5)</td>
</tr>
<tr>
<td>Smoking, current (%)</td>
<td>12.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Diabetes prevalence (%)</td>
<td>6.2</td>
<td>13.8</td>
</tr>
<tr>
<td>Lipid-lowering medication use (%)</td>
<td>11.3</td>
<td>25.0</td>
</tr>
<tr>
<td>Antihypertensive medication use (%)</td>
<td>34.0</td>
<td>57.9</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.1 (19.7)</td>
<td>128.5 (19.6)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.6 (10.5)</td>
<td>74.0 (10.0)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (HDL-C) (mg/dL)</td>
<td>57.9 (16.5)</td>
<td>55.6 (14.0)</td>
</tr>
<tr>
<td>Triglycerides, geometric mean (mg/dL)</td>
<td>121.9</td>
<td>116.4</td>
</tr>
<tr>
<td>Glucose, median and interquartile range (mg/dL)</td>
<td>99 (92–109)</td>
<td>99 (92–110)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>79.9 (13.5)</td>
<td>76.3 (14.9)</td>
</tr>
<tr>
<td>CKD prevalence (eGFR &lt; 60 mL/min/1.73 m²) (%)</td>
<td>7.9</td>
<td>14.5</td>
</tr>
</tbody>
</table>

aData presented as mean (standard deviation) for continuous variables and proportion for categorical variables unless otherwise noted.

bMissing measurements at the KORA F4 visit: four of BMI, three of smoking status, three of diabetes prevalence, one of antihypertensive medication use status, three of lipid lowering medication use status, one of systolic blood pressure, one of diastolic blood pressure.

eGFR = 53.6 mL/min/1.73 m². Subgroup analyses of significant metabolites stratified for baseline CKD revealed smaller effect sizes for these metabolites in individuals with pre-existing disease (Table 3). Supplementary Table S5 displays effect estimates for all metabolites separately for individuals with and without CKD.

Next, we examined all possible ratios of the measured metabolites under the assumption that these ratios may reflect underlying enzymatic conversions between metabolites. Previous evidence shows that some ratios can provide more information than the separate evaluation of their components [8]. Table 2 displays the two multiple-testing-corrected significant metabolite ratios, which contributed information beyond their individual components (P-gain > 139 in the multivariable-adjusted regression analyses). The P-gain reflects the order of magnitude by which the strength of association with eGFR increased when comparing the P-value of a ratio to the lower one of its individual components (see Materials and Methods section). The largest P-gain was noted for the phosphatidylinositol diacyl C42:5-to-phosphatidylinositol acylalkyl C36:0 ratio (P-gain = 1258), which was also the metabolite ratio with the lowest P-value that did not contain creatinine (0.23 mL/min/1.73 m² per SD increment per year, P = 1.5 × 10⁻⁶, Table 2). The ratio with the lowest P-value containing creatinine was creatinine-to-tryptophan (−0.33 mL/min/1.73 m² per SD increment per year, P = 1.7 × 10⁻⁹). The only other multiple-testing-corrected significant ratio, which did not contain creatinine, was the kynurenine-to-tryptophan ratio (P = 1.9 × 10⁻⁶). In addition to its association with annual eGFR change, it was also significantly associated with incident CKD (OR 1.36; 95% confidence interval (CI) 1.11–1.66, P = 2.7 × 10⁻³; Table 2). Notably, both ratios were also nominally associated with rapid annual eGFR decline (>3 mL/min/1.73 m², n = 77 cases): P = 2.5 × 10⁻² for kynurenine-to-tryptophan; P = 3.0 × 10⁻³ for phosphatidylinositol diacyl C42:5-to-phosphatidylinositol acylalkyl C36:0.

Pairwise correlation coefficients with creatinine-based eGFR indicated that neither spermidine (0.06) nor the two ratios (−0.01 for phosphatidylinositol diacyl C42:5-to-phosphatidylinositol acylalkyl C36:0, −0.33 for kynurenine-to-tryptophan) are highly correlated with eGFR at baseline. Neither spermidine nor the two associated ratios showed significant differences in their association with eGFR decline in individuals with and without hypertension or with and without diabetes.

Selected metabolites and ratios previously reported to be associated with enzymes related to kidney function, such as asymmetric dimethylarginine (ADMA), were examined more closely, even if they did not meet the conservative Bonferroni cut-off for statistical significance (supplementary material, Table S3). Effect sizes for these candidates were limited to <0.2 mL change in eGFR per year in our population-based study of mostly healthy individuals.

Finally, the predictive values of clinical parameters and serum metabolites were compared in a separate analysis. Six of the same 11 clinical variables used in the discovery screen for adjustment were selected in an unbiased way to predict incident CKD: age, systolic blood pressure, current smoking, antihypertensive medication use, serum glucose and baseline eGFR. As a measure of accuracy, the area under the receiver-operating curve (AUC) for the clinical model reached 0.81 (95% CI 0.77–0.86). The AUC of the metabolomic-prediction model, based on 35 metabolites selected through an unbiased boosting procedure and listed in supplementary material, Table S4, was similar with 0.82 (95% CI 0.78–0.86). A model combining metabolites selected in addition to the required clinical information included 20 metabolites shown in supplementary material, Table S4, and reached the highest AUC of 0.86, although this was not superior (95% CI 0.83–0.90) to the other models. The receiver-operating curves of the three
models are illustrated in Figure 1. When only the significant metabolite and the two significant ratios were added to the clinical model, discrimination remained unchanged (AUC 0.815 versus 0.815).

While the clinical model predicts the observed number of patients with incident CKD well (Hosmer–Lemeshow test: P-value = 0.22), the combined model required recalibration to improve its overall performance (Hosmer–Lemeshow test after recalibration: P-value = 0.17, AUC unchanged). When comparing the discriminative abilities of the clinical and the recalibrated combined model, there was no significant difference (integrated discrimination improvement: IDI = 0.10, P-value = 0.43).

As no independent validation sample was available, we used a bootstrapping approach to validate the results. The estimated AUC for the combined model (AUC\textsubscript{Bootstr} = 0.80) was only marginally above the model based on clinical information only (AUC\textsubscript{Bootstr} = 0.79).

**DISCUSSION**

While prior studies documented cross-sectional associations between serum metabolites and eGFR in the general population [2, 3], this is—to our knowledge—the first population-based study to assess such associations longitudinally over a time period of years [13, 14].

Serum metabolites and their ratios may be linked to changes in kidney function via several mechanisms. For one, metabolites such as serum glucose may contribute directly to CKD pathogenesis. Second, enzymatic activity may depend on kidney function, e.g. the conversion of glycine to serine by the renal enzyme serine hydroxymethyltransferase. Third, metabolites may be cleared by the kidney, and their serum levels could therefore indicate kidney function, e.g. creatinine. Fourth, metabolites may relate to other processes associated

### Table 2. Metabolites and ratios significantly associated with annual changes in eGFR between KORA visits S4 and F4\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Annual eGFR change (n = 1104)</th>
<th>Incident CKD (n = 1017)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>ES</td>
<td>SE</td>
</tr>
<tr>
<td>Single metabolite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spermidine</td>
<td>−0.24</td>
<td>0.05</td>
</tr>
<tr>
<td>Rations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC aa C42:5/PC ae C36:0</td>
<td>0.23</td>
<td>0.05</td>
</tr>
<tr>
<td>Kynurenine/tryptophan</td>
<td>−0.24</td>
<td>0.05</td>
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</tbody>
</table>

\textsuperscript{a}Adjusted for age, gender, body mass index, systolic blood pressure, smoking, glucose, triglycerides, HDL, antihypertensive medication use, antilipidemic medication use and eGFR, all measured at baseline. Analyses with the outcome of annual eGFR change included baseline CKD cases at the S4 visit. The analyses with the outcome of incident CKD excluded baseline CKD cases at the S4 visit.

### Table 3. Multivariable adjusted associations of significant metabolites, ratios and ADMA with annual eGFR change, stratified by baseline CKD presence (eGFR <60 mL/min/1.72 m\textsupersquare at S4 visit)

<table>
<thead>
<tr>
<th></th>
<th>Probands with baseline CKD (n = 87)</th>
<th>Probands without baseline CKD (n = 1017)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ES</td>
<td>SE</td>
</tr>
<tr>
<td>Metabolites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spermidine</td>
<td>−0.14</td>
<td>0.20</td>
</tr>
<tr>
<td>ADMA</td>
<td>−0.19</td>
<td>0.18</td>
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<tr>
<td>Rations</td>
<td></td>
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<tr>
<td>PC aa C42:5/PC ae C36:0</td>
<td>0.15</td>
<td>0.16</td>
</tr>
<tr>
<td>Kynurenine/tryptophan</td>
<td>−0.14</td>
<td>0.15</td>
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</tbody>
</table>
with CKD development, such as oxidative stress or inhibition of endothelial nitric oxide synthesis [15].

Previously, we identified certain acylcarnitines such as decadienylcarnitine to be cross-sectionally associated with lower eGFR in a larger sample of the KORA study population [3]. Higher concentrations of decadienylcarnitine were nominally associated with kidney function decline in this longitudinal study, but did not pass the multiple-testing-corrected significance threshold (supplementary material, Table S3). Some previously described CKD-associated metabolite markers of oxidative stress (e.g. the methioninesulfoxide-to-methionine ratio) or nitric oxide production (e.g. the citrulline-to-arginine ratio) also did not associate significantly with kidney function decline in this prospective study of the general population (supplementary material, Table S3) [16, 17].

One of the significant metabolites identified here, the polyamine spermidine, was described in smaller cross-sectional studies to be either elevated or decreased in CKD cases compared with controls [13, 14]. While in our study, baseline spermidine levels showed an insignificant association with baseline eGFR \(0.84 \text{ mL/min/1.73 m}^2\) per SD increment; \(P = 0.02; n = 1104\), elevated baseline spermidine levels were significantly associated with eGFR decline over time. Conceptually, metabolites playing a role in disease etiology may be more strongly associated with longitudinal eGFR decline (e.g. spermidine), while metabolite markers of glomerular filtration may be more strongly associated with cross-sectional eGFR (e.g. decadienylcarnitine).

The kynurenine-to-tryptophan ratio was strongly associated with both eGFR loss and incident CKD. This ratio is thought to reflect the degradation of tryptophan by the inducible enzyme indoleamine 2,3-dioxygenase, which was reported to associate cross-sectionally with CKD severity, uremic symptoms, inflammation, obesity, blood pressure and atherosclerosis [18–21]. The direction of the association for the kynurenine-to-tryptophan ratio with loss of eGFR and higher disease incidence found in our longitudinal analyses are thus in accordance with prior studies published by other investigators. Its individual components (kynurenine and tryptophan) did not show a significant association with eGFR change. This indicates substantial information can be gained by linking the two components and supports a role of the aforementioned conversion enzyme in kidney disease. The other significant ratio of phosphatidylcholine diacyl C42:5/ phosphatidylcholine acylalkyl C36:0 may be related to the enzyme lipoprotein-associated phospholipase A(2) (Lp-PLA(2)), which was described to be associated with important clinical outcomes such as CKD progression and cardiovascular events (Box 1) [22].

Prediction models containing either baseline metabolite parameters or commonly used clinical parameters contained similar predictive information as measured by the AUC. While this emphasizes a remarkable capacity of a serum metabolite panel to predict disease to a similar extent as clinical parameters without having any additional information about the patient, it does not support the routine use of metabolomic measurements for prediction. Along these lines, it has been observed for other markers identified from high-throughput screens that they currently do not improve prediction of common complex diseases such as CKD [23, 24].

Our study’s strengths are a large sample size, a long-term follow-up, the exact metabolite quantification and a broad spectrum of molecular classes examined. Potential limitations include the lack of an independent replication sample, a relatively healthy study population with potential imprecision in the higher range of estimated GFR, creatinine measurements at only two points in time and residual confounding. As to the best of our knowledge, there are no other studies with the same metabolite panel measured at baseline and eGFR measured years later. We subjected our findings to a rigorous correction for multiple testing, which should greatly reduce false-positive results.

In summary, baseline concentrations of serum spermidine, the kynurenine-to-tryptophan and the phosphatidylcholine diacyl C42:5-to-phosphatidylcholine acylalkyl C36:0 ratios were associated with a change in kidney function over subsequent years in the general population. It remains to be elucidated if any of these metabolites have a direct etiologic role or indicate early-stage disease processes.

**Supplementary Data**

Supplementary data are available online at http://ndt.oxfordjournals.org.

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**CONFLICT OF INTEREST STATEMENT**

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**REFERENCES**


<table>
<thead>
<tr>
<th>Significant metabolites</th>
<th>Related enzyme(s) or proteins</th>
<th>Postulated role in pathophysiology</th>
<th>Reported associations with clinical parameters</th>
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<tbody>
<tr>
<td>Spermidine</td>
<td>Spermidine synthase; spermine oxidase; spermidine/spermin-N¹-acetyltransferase</td>
<td>Altered polyamine metabolism</td>
<td>CKD, diabetes, obesity, inflammation, renal ischaemia reperfusion injury, NSAID use, chemotherapy [13, 14, 25–27]</td>
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<th>Significant ratios</th>
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<tbody>
<tr>
<td>Phosphatidylcholine diacly C42:5/ phosphatidylcholine acylalkyl C36:0</td>
</tr>
<tr>
<td>Kynurenine/ tryptophan</td>
</tr>
</tbody>
</table>

**Box 1. Biologic information about metabolites significantly associated with kidney function decline and related metabolite conversion enzymes.**

NSAID, nonsteroidal anti-inflammatory drugs. Cited references provide information about the directions of the reported associations.


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