Renal function and cognition in the 1932 Scottish Mental Survey Lothian cohort

Sir—Severe uraemia is associated with cognitive impairment and dementia [1, 2]. At a moderate level, elevated serum creatinine is associated with an increased risk of vascular dementia, though not Alzheimer’s disease [3]. This increase has been attributed to cardiovascular disease that often accompanies moderate renal impairment, but adjusting for cardiovascular risk factors does not completely abolish the association. [3]. It is possible that any renal-cognitive impairment association reflects microvascular disease [4], in particular, that associated with cerebral white matter lesions [5]. There is a paucity of data about any association between cognitive function and renal function within the normal range in older people, though an association was found for menopausal women [6]. Even if an association exists, direction of causality remains undetermined. Children with lower IQs are known to have higher blood pressures in middle age, even after adjusting for social class, smoking and gender [7], and this, in turn, may lead to later decrements in renal function. Thus, it is not clear whether prior cognitive ability contributes to later renal function or whether there is reciprocal influence. We investigated the association between renal function and cognitive function in a unique cohort of older people who had early life mental ability data that allowed potential causal pathways to be elucidated.

Methods

Sample

The sample has been extensively described previously [8]. The Scottish Mental Survey of 1932 (SMS1932) tested mental ability in people born in 1921 who attended schools in Scotland on June 1, 1932 (n = 87,498). The SMS1932’s Moray House Test (MHT) was validated against the Stanford Binet test and includes verbal reasoning, numerical, spatial and other items. From 1999 to 2001, we traced and retested 550 people from Edinburgh who were born in 1921 (the Lothian Birth Cohort 1921). Uniquely, in Scotland, the childhood cognitive ability of the subjects tested here can be described with reference to the entire population. The mean (SD) raw MHT score for Scotland was 34.5 (15.5). The mean of the scores for the children tested in Edinburgh city schools was 37.3 (14.8). The mean of the scores for those who survived and were recruited into the Lothian Birth Cohort of 1921 was 46.4 (12.1). We repeated the original MHT, converting it to age-adjusted IQ scores, together with the Mini-Mental State Examination (MMSE), Raven’s Standard Progressive Matrices (RPM), Verbal Fluency (VF) and Wechsler Logical Memory (LM), totalling immediate and delayed scores from two stories. The study was conducted with permission from the local research ethics committee. All participants gave written informed consent and were living independently in the community; none was on renal replacement therapy.

Measures

Diagnoses and drugs were classified as previously described [9] to include a personal history of cardiac, cerebrovascular, non-cardiac and non-cerebrovascular vascular disease (e.g. peripheral arterial disease, abdominal aortic aneurysm etc.), hypertension and diabetes, and also use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors. Non-fasting blood tests included serum creatinine and glycated haemoglobin (HbA1c). We also genotyped the ACE intron 16,250 bp insertion (I)/deletion (D) polymorphism [10]. We estimated glomerular filtration rate (GFR) using the modification of diet in renal disease (MDRD) formula as studies suggest this is the method of choice in older people [11–13].

Statistical analysis

The MDRD formula includes age and gender as terms in calculating GFR. Hence testing for any association between MDRD-estimated GFR and age or gender would identify spuriously significant effects. Fortunately, all subjects were born in the same year. To avoid spurious gender associations, we analysed data for men and women separately. GFR data did not significantly deviate from a normal distribution for either men or women so parametric tests were appropriate. For those analyses involving mental test scores of participants aged 79, we excluded people with dementia or MMSE scores <24 as previously [9]. All analyses were performed using the SPSS 14.0 statistical package.

Results

We obtained serum creatinine estimates for 529 of the 550 participants. The 225 men had a mean GFR of 72 (s.d. 16) ml/min and the 304 women had a mean GFR of 67 (s.d. 16) ml/min. GFR correlated significantly (P<0.05) and positively with Raven’s Matrices (r = 0.14), VF (r = 0.15), and age 79 MHT (r = 0.16) in men, but only with VF in women (r = 0.13) (Table 1). GFR also correlated with age 11 MHT IQ in men (r = 0.15); after adjusting for childhood IQ, none of the correlation coefficients between GFR and cognitive tests taken at the age of 79 remained significant (Table 1). Since age 11 IQ was associated with GFR in old age in men, we proceeded to linear regression with stepwise entry
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Table 1. Pearson correlation coefficients (∗ indicates P<0.05) between GFR and cognitive test scores, unadjusted and adjusted for vascular risk factors (blood pressure, HbA1c and cholesterol) and age 11 IQ

<table>
<thead>
<tr>
<th>Variable</th>
<th>Raw correlation</th>
<th>Adjusted for vascular risk</th>
<th>Adjusted for age 11 IQ</th>
<th>Raw correlation</th>
<th>Adjusted for vascular risk</th>
<th>Adjusted for age 11 IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.012</td>
<td>−0.027</td>
<td>0.004</td>
<td>0.051</td>
<td>−0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>RPM</td>
<td>0.14∗</td>
<td>0.15</td>
<td>0.077</td>
<td>0.001</td>
<td>−0.052</td>
<td>−0.054</td>
</tr>
<tr>
<td>VF</td>
<td>0.15∗</td>
<td>0.13</td>
<td>0.11</td>
<td>0.13∗</td>
<td>0.13∗</td>
<td>0.11</td>
</tr>
<tr>
<td>LM</td>
<td>0.049</td>
<td>0.040</td>
<td>0.022</td>
<td>0.043</td>
<td>−0.001</td>
<td>0.017</td>
</tr>
<tr>
<td>Age 79 IQ</td>
<td>0.16∗</td>
<td>0.070</td>
<td>0.057</td>
<td>0.079</td>
<td>0.031</td>
<td>0.031</td>
</tr>
<tr>
<td>Age 11 IQ</td>
<td>0.15∗</td>
<td>0.16∗</td>
<td>−0.059</td>
<td>0.059</td>
<td>0.043</td>
<td>−0.043</td>
</tr>
</tbody>
</table>

(∗ indicates P<0.05) with GFR as the dependent variable. For men, significant independent variables were blood pressure (β = 0.17, P = 0.023), social class (β = −0.17, P = 0.025), ACE inhibitor use (β = −0.16, P = 0.050) and personal history of hypertension (β = −0.15, P = 0.050) accounting for 11.5% of GFR variance compared with 9.7% for the model with age 11 IQ substituted for social class. Adding age 11 IQ to the optimum model did not alter adjusted R², but reduced social class β to 0.12. No other variable significantly improved the model except HbA1c for those participants where it was available. GFR in women was significantly associated with body mass index (β = −0.17, P = 0.006), a personal history of hypertension (β = −0.14, P = 0.025) and NSAID use (β = −0.13, P = 0.034) only accounting for 7.3% of variance. There were no significant differences between men and women for personal history of hypertension (P = 0.18), diabetes (P = 0.84), NSAID use (P = 0.64), or social class (P = 0.066), but men were more likely to be taking an ACE inhibitor (P = 0.015).

Discussion

For men, and to a lesser extent for women also, there is a small but significant association between cognitive and renal function in old age within the normal range. However, this association is fully explained in men by the correlation between age 11 IQ and GFR at the age of 79. We have suggested several causal pathways that may explain relationships between childhood IQ and later life morbidities [7]. First, genes that influence childhood IQ may also determine GFR in old age. We looked at ACE polymorphisms as a possible candidate, but found no effect, probably because of low statistical power. There are many other potential candidate genes [14], but if these explained all of the effect of age 11 IQ on late-life GFR, its association should not disappear when other explanatory variables are included in models. The same could be said of our second causal pathway, events preceding age 11, such as foetal programming, that can be considered as a ‘common cause’. The final pathway involves environmental variables after age 11, which may themselves interact with genetic predisposition. This association between age 11 IQ and GFR disappeared once social class was adjusted for.

Childhood IQ is a key influence on adult social class [15] and this probably forms one causal pathway linking childhood IQ to late-life renal function. The effect of social class is not explained by vascular disease, smoking habit or alcohol use; so it is possible that it relates to adverse environmental exposures in the working environment or diet. A difference between white men and women in the effect of area socio-economic status on renal function was found previously in the Atherosclerosis Risk in Communities study [16]. The relationship with blood pressure, personal history of hypertension and HbA1c is consistent with renal impairment being a manifestation of the metabolic syndrome [17]. There was a difference between the effects of ACE inhibitors and NSAIDs on men and women. No effect of NSAIDs on renal function was found in the large Physicians’ Health Study [18], where all the physicians were middle-aged men, whilst a study in younger women did detect an adverse effect [19]. ACE inhibitors may contribute to acute worsening of renal function in the elderly, but they may confer specific renoprotective effects beyond their antihypertensive effect alone [20].

One limitation of our study is that we estimated GFR from serum creatinine rather than measuring it directly. Such estimations may be unreliable in obese people [13]. Around 15% of the sample had body mass index (BMI) >30 kg/m², but results were essentially unaltered when these participants were excluded from the analysis, except that BMI was no longer associated with GFR in women. Nevertheless, if renal impairment is part of an underlying metabolic syndrome, it may have been more appropriate to measure waist circumference [21]. Direct measurement of GFR would have allowed quantification of the effects of age, though not applicable in this narrow cohort, and gender. Future studies might also wish to collect more detailed work-related exposures to assess any contribution of these to renal function.

In conclusion, these unique data reveal that the relationship between cognitive and renal function in old age needs to be considered in a life-course context. Renal function in old age is determined not only by current hypertension or HbA1c, but also previous exposures indicated by social class, that in turn reach back to cognitive status in childhood.
Key points
• Renal function correlates significantly with cognitive function in healthy older people.
• This correlation becomes non-significant after adjusting for the positive correlation between estimated GFR and childhood IQ.
• The effect of childhood IQ on renal function in old age is mediated by social class related factors.
• The relationship between cognitive and renal function in old age needs to be considered in a life-course context.

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Conflicts of interest
None.

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