Mildly reduced kidney function and albuminuria

Valorization addendum

Apart from education and research, knowledge valorization is considered to be a core activity of universities.[1] In this regard, knowledge valorization is defined as "the process of creating value from knowledge, by making knowledge suitable and/or available for societal (and/or economic) purposes, and suitable for translation into competitive products, services, processes and new entrepreneurship" (adapted definition based on the National Committee Valorization 2011:8). This addendum describes how society may benefit from the results presented in this dissertation.

Chronic kidney disease (CKD) affects 8-16% of the population worldwide.[2] For the Netherlands, the prevalence has been estimated at 10.4%,[3] which means that about 1.8 million of its approximately 17 million citizens have CKD. CKD imposes a significant economic burden on society. This includes costs from dialysis treatment and transplantation in end-stage renal disease, and from the management of cardiovascular disease (CVD) and other adverse health conditions related to CKD in all CKD stages. At least as important are the consequences of CKD related adverse health conditions for quality of life.

This dissertation expands the evidence for associations of reduced estimated glomerular filtration rate (eGFR) and albuminuria, which define CKD,[4] with (chronic) health problems other than the classic CVD manifestations. In addition, it provides further evidence for the hypotheses that generalized endothelial dysfunction explains the unfavorable associations of albuminuria, and that physical activity and sedentary behavior may be independent targets in the prevention of reduced eGFR and albuminuria. The associations reported already appeared at levels of eGFR and albuminuria which do not fulfill the current CKD criteria, thus at the levels which are commonly observed in the general population. Therefore, the results presented in this dissertation may not only be relevant to individuals with CKD and their health care providers, but for individuals in the general population and health care policy makers as well. In addition, the results may be relevant to the pharmaceutical industry.

In the short-term, the results presented in this dissertation may lead to at least three kinds of research initiatives, which may in the long-term contribute to a reduction in the adverse health conditions related to lower eGFR and higher albuminuria.

First, future longitudinal studies are required to confirm the results presented in this dissertation and to provide more insight into the underlying mechanisms. With regard to the latter, it is, for example, important to examine the relative contribution of cardiac production and (renal) elimination to the associations of eGFR with the biomarkers of cardiac injury. In addition, future studies may examine whether vascular dysfunction in the brain indeed explains the associations of albuminuria with lower cognitive performance and depression, as hypothesized in this dissertation.

Second, this dissertation may contribute to the discussion on the implementation of combined screening and early treatment programs for albuminuria. Such programs have been proposed for the general population to reduce the societal and health impact of CKD.[5] Indeed, albuminuria screening may be a cost-effective approach to prevent end-stage renal disease and, in particular, CVD.[6] However, its cost-efficacy is controversial and seems to depend on the assumptions made in the analyses.[7] An important consideration is the outcomes that may be prevented by treating individuals with albuminuria.[6] In this regard, the results presented in this dissertation, if confirmed, suggest that future studies on the cost-efficacy of albuminuria screening may not only consider the prevention of end-stage renal disease and CVD events, but the prevention of other adverse health conditions, for example dementia and depression, as well. Another important consideration is the efficacy of treatment with renin-angiotensin system inhibitors in individuals with albuminuria.[7] Renin-angiotensin system

inhibitors lower albuminuria and have been shown to reduce the risk of end-stage renal disease and nonfatal CVD events. However, their effects on mortality and fatal CVD events have been questioned.[8] The results presented in this dissertation support the hypothesis that individuals with albuminuria benefit most from interventions which improve not only renal endothelial function and hemodynamics, but systemic endothelial function as well. In this regard, future studies could examine the effects of currently available medications with pleiotropic effects on the endothelium, such as 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase inhibitors (*i.e.*, statins),[9] on CVD and other adverse health conditions in individuals with albuminuria. In addition, the effects of medications which directly target endothelial function may be examined, for example the endothelin antagonist atrasentan, which has already been shown to reduce albuminuria.[10] Herein lies a role for the pharmaceutical industry.

Third, the efficacy of preventive strategies that target lifestyle factors at the general population level to prevent reduced eGFR, albuminuria and their associated adverse health conditions should be examined. The results presented in this dissertation suggest that reducing the time spent sedentary as well as increasing physical activity could be valuable targets for such preventive strategies. However, the amounts of physical activity and sedentary time that are required to achieve a clinically significant effect on eGFR and albuminuria as well as the 'ideal' pattern of sedentary behavior are unknown and deserve further study. This also pertains to the strategies to achieve the required behavioral alterations. Eventually, the results of future studies on this topic may be implemented in national guidelines on physical activity and sedentary behavior. In this regard, a national guideline on physical activity already exists for other outcomes.[11] In addition, a national guideline on sedentary behavior has been recommended based on the unfavorable associations of sedentary behavior with several metabolic outcomes.[12]

The research initiatives described above may be translated into several PhD projects. A close collaboration between researchers from several disciplines is required to disentangle the associations of eGFR and albuminuria with extrarenal disease. In addition, combining data from multiple (existing) cohorts will increase the statistical power to study these associations in the general population and improve generalizability in a way that efficiently utilizes available resources. Importantly, in particular the first research initiative described above calls for studies with a detailed characterization of their participants. In this regard, follow-up data of The Maastricht Study are eagerly awaited.

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