Epidemiology of chronic kidney disease in Europe
Brück, K.

Citation for published version (APA):
Brück, K. (2016). Epidemiology of chronic kidney disease in Europe

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 4:

Translational research in nephrology: chronic kidney disease prevention and public health

Katharina Brück, Vianda S. Stel, Simon Fraser, Moniek C.M. De Goeij, Fergus Caskey, Ameen Abu-Hanna and Kitty J. Jager

Clinical Kidney Journal. 2015; 8 (6), 647–655
http://ckj.oxfordjournals.org/content/8/6/647.full?etoc
Introduction

Chronic kidney disease (CKD) is increasingly recognized as a global public health problem. People with CKD are at risk of developing end stage renal disease (ESRD) and have a notably increased risk of cardiovascular disease (CVD) and mortality (1-4). From 1990 to 2010 the age-adjusted death rates attributable to CKD have increased by 15% (5) and CKD is now the 19th leading cause of life years lost (3). While some of this increase may be attributable to increased identification and coding, other factors such as demographic transition to older population profiles and rural to urban population shift in low and middle income countries must be considered (6).

Worldwide an estimated 8-16% of the general population has CKD (7). The prevalence of CKD prevalence increases with age to about 30% in people aged over 70 years (8, 9). Added to this is an anticipated increase in CKD prevalence as a result of the ongoing epidemics of diabetes, hypertension and obesity (8), all of which (both individually and in combination) are important risk factors for CKD (2). In addition to the implications for morbidity and mortality, the growing prevalence of CKD has significant implications for health and social care systems, particularly considering the high cost of renal replacement therapy, the greatest burden of which may in future be felt in developing countries (3).

Although dependent to some extent on the causal pathophysiology, in principle, the development of CKD and its complications can be (partly) prevented or delayed (7). In 2013 the World Health Organization’s (WHO) Global Action Plan for the Prevention and Control of Non-communicable Diseases (NCDs) 2013-2020 was adopted (10). In this plan, the WHO lists nine public health targets which will help to reduce the global burden of NCDs by targeting both lifestyle factors and specific NCDs (Figure 1) (10). Although CKD is not a direct target in this WHO action plan, the plan does acknowledge the link between major NCDs, such as diabetes and hypertension, and CKD. Moreover, five of the WHO targets are aimed at important CKD risk factors namely: physical inactivity (11), high dietary salt intake (12), smoking (13), diabetes and hypertension (2). In this narrative review, we will review how the available evidence on these important CKD risk factors is being translated into the implementation of measures to prevent CKD and its complications and to improve public health.

ABSTRACT

This narrative review evaluates translational research with respect to five important risk factors for chronic kidney disease (CKD): physical inactivity, high salt intake, smoking, diabetes and hypertension. We discuss the translational research around prevention of CKD and its complications both at the level of the general population, and at the level of those at high risk, i.e. people at increased risk for CKD or CKD complications.

At the population level, all three lifestyle risk factors (physical inactivity, high salt intake, and smoking) have been translated into implemented measures and clear population health improvements have been observed. At the ‘high risk’ level, the lifestyle studies reviewed have tended to focus on the individual impact of specific interventions, and their wider implementation and impact on CKD practice are more difficult to establish. The treatment of both diabetes and hypertension appears to have improved, however the impact on CKD and CKD complications was not always clear. Future studies need to investigate the most effective translational interventions in low and middle income countries.
hypertension (2). Thus we will consider both primary and secondary prevention strategies for CKD in a translational research framework.

**Public health translational research framework**

There is no clear consensus regarding the term translational research (15). Traditionally it concerns the translation from “bench-to-bedside”, i.e. using basic science results to develop new treatments or diagnostics for patients (15). In public health terms translational research is commonly interpreted as the translation of “research into practice”, i.e. ensuring that new research knowledge will reach the intended patients and populations and that it is implemented correctly with the prospect of improving health (15). Both these traditional basic science and public health perspectives on translational research have been incorporated into various linear frameworks (16-18), such as the framework described by Khoury et al. (16) which distinguishes five phases of translational research (see box):

<table>
<thead>
<tr>
<th>Phase 0: description and discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1: from discovery to health applications</td>
</tr>
<tr>
<td>Phase 2: from health application to evidence guidelines</td>
</tr>
<tr>
<td>Phase 3: from guidelines to health practice</td>
</tr>
<tr>
<td>Phase 4: from health practice to population health outcomes</td>
</tr>
</tbody>
</table>

An alternative nonlinear framework has been proposed by Ogilvie et al. (19). This framework was developed specifically for the translation of public health research (19). They argue that translating research into improvement of public health involves a much wider scope than the translation of research by researchers alone, as the practice to be influenced is not limited to clinical practice or public health practice (19). We have chosen to use an adaptation of this framework by Ogilvie et al. as the outline for our review, because this framework reflects the complex interactions involved in translating health research into public health improvement (Figure 2).

In recent years, translational research has received increased attention from funding bodies such as the National Institute for Health Research (NIHR) in the UK (18). However, there is evidence that the majority of funding for translational research has still historically been assigned to the translational from bench to bedside (20) rather than on implementation (21) or population health impact. As a consequence of this emphasis, most translational research focuses on this bench to bedside translation (15).
Nevertheless one may argue that the translation from ‘research to practice’, e.g. implementation into health practice, has the potential to benefit more people. It is important to remember that the greatest benefit to population health may not be achieved by simply targeting those at highest risk. To cite Rose “A large number of people at a small risk may give rise to more cases of disease than the small number who are at high risk” (22). We will therefore consider population level measures and their impact as well as ‘high risk’ level measures and their impact.

**LIFESTYLE FACTORS**

**Physical inactivity**

**Population level measures**

Many observational studies have shown that in healthy subjects regular physical activity is associated with reduced morbidity and all-cause and cardiovascular mortality, leading to the development of general population physical activity guidelines in many countries (11, 23, 24). Increasing physical activity at population level is a complex topic encompassing many different strategies including policies, advocacy, environmental/infrastructure changes and awareness and education (23). These strategies fit in the ‘Public Realm’ box of the Ogilvie model (Figure 2). Several governments have implemented campaigns to increase physical activity of their population, such as the ‘exercise 30 minutes a day’ and ‘10,000 steps a day’ campaigns in the Netherlands and Belgium respectively (25, 26). In line with this, the WHO Global Action Plan for the Prevention and Control of Non-communicable Diseases aims for a “10% relative reduction in the prevalence of physical inactivity” (10).

There is a wide variety of methods used to increase physical activity levels of the population, from changing infrastructure of urban areas to methods of influencing behavioural change. It falls outside the scope of this review to describe all of these in detail, however they are of great relevance for both the general population and for people at the high risk level. One specific example is the recent development of the increasing availability and use of mobile health applications (‘apps’) and other electronic devices to monitor and adjust physical activity and other health related behaviour. This has prompted the U.S. Food and Drug Administration (FDA) to publish guidance on mobile medical apps for the industry in 2013 (27). This guidance clarifies which apps are considered to be subject to the FDA authority and the regulatory requirements that will apply to such apps. A report by Research2guidance, predicted that by 2015, 500 million people will be using mobile healthcare applications (28). The development and use of apps to monitor physical activity may likely influence public health awareness and perhaps modify health related behaviour of both the general population and patients. Yet the effectiveness of these apps in increasing physical activity needs further study.
In 2002, 31% of the adult European population reported regularly undertaking sufficient physical activity, i.e., 30 minutes of moderate physical activity ≥5 times a week (29). Several European countries have published physical activity trend data, which fits into the box ‘health-related behaviour’ of the Ogilvie model (Figure 2). In the Netherlands, the percentage of the population fulfilling the minimum physical activity level criteria has increased from 52% to 62% in the period from 2001 to 2011 (30). In the UK, from 1997 to 2012, the percentage of men and women meeting the physical activity criteria increased from 32% to 43% and 21% to 32% respectively (31). Despite the increased physical activity seen in both the Netherlands (32) and the UK (33), obesity prevalence is still increasing in both countries. In the UK the obesity prevalence increased between 1993 to 2012 from 13.2% to 24.4% and 16.4% to 25.1% in males and females respectively (33). These data suggest that interventions to increase physical activity are effective in increasing the physical activity level, but not in decreasing the obesity prevalence in the general population (34).

However, increased physical activity is related to various other health benefits such as improved glycaemic control, reduced blood pressure and reduced cardiovascular risk (35). In terms of interventions, a recent systematic review by Laine et al. concluded that, community rail trails, pedometers and school health education programs were the most cost effective measures to increase physical activity on a population level (36). Prior to this, Roux et al. had modelled the cost effectiveness of seven community based physical activity interventions, such as community wide campaigns and the creation of physical activity information and opportunities, and concluded that all seven strategies considered were cost effective at reducing the incidence of chronic diseases such as coronary heart disease, ischemic stroke, and type 2 diabetes (37).

Additional high risk level measures
Although multiple studies report beneficial impact of physical activity in people with CKD (38, 39), evidence based guidelines with specific exercise recommendations for people with CKD are lacking (40, 41). Nonetheless, multiple guidelines include an exercise recommendation for people with CKD based on low grade evidence (1, 42, 43), which fit into the box ‘Professional Practice’ of the Ogilvie model (Figure 2). For example, Kidney Disease Improving Global Outcomes (KDIGO) recommends to encourage people with CKD to undertake physical activity compatible with cardiovascular health and tolerance 5 times a week for at least 30 minutes (1). Few studies examined exercise adherence by people with CKD (41). In a randomized controlled trial in which people with CKD received eight weeks of supervised training followed by ten months of home based training, self-reported adherence dropped from 70% during the supervised training to 53% at the end of the ten months home based training period (44).
one or multiple products, nine of which were in Europe (49). All nine European countries reduced the salt content of bread, ranging from a 6% reduction in Belgium to 29% reduction in Ireland (49). Finland started salt reduction efforts as early as 1978 including mandatory warning labels for food products high in salt (50). By 2002 the Finish average salt intake had reduced from 12 grams to 9 grams per day (50). These studies on salt intake fit within the box ‘Health-related behaviour’ (Figure 2).

Bibbins-Domingo et al. projected that even minor reductions in dietary salt intake (e.g. 1 gram a day) through population wide salt reduction strategies, would be cost-effective to reduce cardiovascular events and lower medical costs (51). From 1970 to 1995 the cardiovascular mortality decreased with 65% (52) in Finland. According to Varttainen et al., 32% and 38% of the stroke mortality reduction was explained by a decrease in diastolic blood pressure for males and females, respectively (53). The reduction in mortality from ischaemic heart disease could be explained by a decrease in diastolic blood pressure in 15% and 31% of the males and females respectively (54). Within the general population, dietary salt reduction reduces the risk of cardiovascular events and possibly all-cause mortality (55).

Additional high risk level measures
Although evidence based clinical practice guidelines for people with CKD generally recommend reduction in dietary salt intake (56), the various guidelines report different salt targets. KDIGO recommends a salt intake of less than 2 grams/day (57) and the Canadian Society of Nephrology recommends sodium targets depending on hypertensive status (42). These guidelines can be considered in the ‘Professional practice’ box of the Ogilvie model (Figure 2). Restricting dietary salt intake can be challenging and, in clinical practice, recommended salt targets are often not achieved in people with CKD (58, 59). This may be influenced by insufficient emphasis on salt reduction by care providers (12), yet is likely also influenced by patient non adherence (59). Dietary salt recommendations can be confusing for patients and general population alike, and adhering to recommended targets is difficult for individuals. Therefore interventions at the population level, such as legislation influencing food manufacturers to reduce salt content, are the most likely to succeed in reducing dietary salt intake of both the general population and people with CKD.

High risk level impact
In people with CKD, salt reduction is a low risk and cost effective strategy to reduce blood pressure as compared to blood pressure reducing drugs (56). Salt restriction reduces both hypertension and proteinuria in people with CKD (56, 60). However a recent post hoc analysis of the ONTARGET and TRANSCEND trial found no association between low sodium diet and risk of ESRD (61). Unfortunately there are no studies on the effect of salt reduction on mortality (56).

Smoking
Population level measures
Smoking is associated with an increased risk of CKD in the general population (62). The WHO target is “a 30% relative reduction in prevalence of current tobacco use in person aged 15+ years” (10). In Europe there are various, ‘Public realm’, measures against smoking, such as specific excise taxes on tobacco (63) and the ban on tobacco advertising in the entire European Union (EU) (63). Currently, 17 EU countries have smoke free laws in place, such as a ban on smoking in public spaces and in the workspace (64). Additionally, the EU has developed multiple anti-smoking campaigns (65).

Population level impact
There is some conflicting evidence on the effectiveness of mass media campaigns in reducing smoking uptake and prevalence (66). While the vast majority are shown to be effective (66, 67), there is a need to be careful about the campaign message and mode of delivery in order to be effective (66). Policies which ban smoking in public places and the workspace have been shown to be effective in reducing tobacco consumption (68, 69). However, according to The Lancet Commissions, specific excise taxes are the most effective intervention against tobacco use and related non-communicable diseases at population level (70). The WHO estimated that doubling prices on tobacco by raising specific excise taxes, would lead to an increase in tobacco tax revenues of $100 billion (71), despite reducing tobacco consumption by one third (63). In contrast, reducing tobacco consumption by a third through other measures would actually lead to an estimated decrease in tobacco tax revenue of $100 billion (71). Tobacco specific excise taxes are therefore highly cost effective.

Recently Bilano et al. reported the global trends for tobacco use (72). From 2000 to 2010, tobacco use decreased in men in all 31 European high income countries, but in women tobacco use decreased only in 27 of these countries (72). Smoking cessation appears to reduce mortality (56).
cessation counseling is less often promoted as kidney function declines (75). Another study performed in patients at risk for CVD, including 923 CKD patients, found that in Canadian primary care about 50% of smokers received smoking cessation counseling (76). Plenty of residual opportunity therefore remains to promote smoking cessation in clinical contexts.

High risk level impact
To our knowledge no studies are available on the effectiveness of smoking cessation strategies in people with CKD (13). Although only few studies have investigated the effect of smoking cessation on renal function in people with CKD, all studies found a positive effect (13).

NON COMMUNICABLE DISEASES AS RISK FACTORS

Diabetes

CKD screening in diabetic patients
Screening for kidney disease in people with diabetes is now generally recommended (77). Moreover, several studies have suggested that CKD screening is cost effective in this context (78, 79). Nonetheless, adherence to CKD screening guidelines varies markedly across countries and between physicians (80, 81).

Treatment of diabetes
Multiple studies have shown that the development and progression of albuminuria in diabetic subjects can be prevented through strict glycaemic control and the use of angiotensin converting enzyme inhibitors (ACEi) (82-84). Accordingly, the use of glycaemic control medication and ACEi in diabetic subjects has increased over the years (85, 86). Golan et al. have proposed that treating all middle aged type 2 diabetics with ACEi is the most cost-effective strategy to slow progression to end stage renal disease (ESRD) (79).

The impact of this improved treatment of diabetes on CKD and its complications is unclear. Some studies have described the trends in diabetic kidney disease prevalence, yet these are influenced by both incidence and survival (85, 86). There are some reports on the change of renal replacement therapy (RRT) incidence for ESRD due to diabetes. From 1996 to 2006 the incidence of RRT for ESRD in diabetics decreased in the United States (87). This is in line with results from Europe, in which the incidence of RRT for ESRD due to type 1 and 2 diabetes in the general population decreased between 1998 and 2011 (88). Although this decline may be due to slower progression of CKD caused by improved treatments and earlier detection, it may also be partly explained by a change in renal replacement initiation practices.

Hypertension

CKD screening in hypertensive patients
Almost all guidelines recommend screening for CKD in hypertensive subjects (89, 90). Boulware et al. have shown that screening in hypertensive subjects is cost-effective irrespective of age (91).

Treatment of hypertension
Although hypertension increases the risk of developing CKD, there is no clear evidence that blood pressure reduction lowers that risk (92, 93). Importantly, hypertension is among the biggest single disease risk factors for global disease burden (3) and therefore hypertension treatment should be a high priority at the population level even if evidence of its impact on CKD incidence is limited. In CKD patients, treatment of hypertension is recommended to reduce CKD progression and lower cardiovascular disease risk (1). Medication adherence to antihypertensive agents within CKD patients has been estimated to be around 67% (94).

Using data from the Health Survey for England, Aitken et al. observed an increase in the use of antihypertensive drugs in hypertensive subjects in England, between 2003 and 2008 (86). In this same period, the systolic and diastolic blood pressure decreased in the hypertensive population while the CKD prevalence within the hypertensive population stayed approximately the same (86). In CKD patients there is evidence that more could be done to improve blood pressure control. Several studies have identified that recommended blood pressure targets are only achieved in less than 50% of patients (58, 95). A study in CKD patients in primary care found that older age, greater albuminuria levels and diabetes were all associated with poorer blood pressure control (95).

Conclusion
In this narrative review we have discussed five important CKD risk factors which are targeted by the WHO action plan against NCDs: physical inactivity, high dietary salt intake, smoking, diabetes and hypertension. Considering the framework proposed by Ogilvie et al. we have described measures involving various stakeholders, such as policy makers, health practitioners and the food industry. Thus highlighting the importance of seeing the ‘big picture’ when reviewing the translation of research in the context of public health.

Lifestyle factors
At the population level, all three lifestyle risk factors were translated to implemented measures, varying from campaigns promoting physical activity and reducing dietary salt intake to specific excise taxes on tobacco. The implemented lifestyle measures appeared to have a positive impact at the population level as physical inactivity, dietary salt intake and smoking were all reduced after implementation of population wide measures. The
Of note, we have discussed five important risk factors for CKD, but there are multiple other important factors and measures relevant to the prevention of CKD and its complications, such as acute kidney injury (96), alcohol use (97), (dietary) interventions for obesity (7). Since in low and middle income countries the burden of CKD and related non-communicable diseases is increasing rapidly (3) there is an urgent need for understanding the most effective translational interventions in these countries.

Acknowledgements:
Joost Daams (Collection manager, medical information specialist Medical Library AMC)


34. Malhotra A, Noakes T, Phinney S. It is time to bust the myth of physical inactivity and obesity: you cannot outrun a bad diet. Br J Sports Med. 2015.


44. Malhotra A, Noakes T, Phinney S. It is time to bust the myth of physical inactivity and obesity: you cannot outrun a bad diet. Br J Sports Med. 2015.


43. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2015;30 Suppl 2:ii1-142.


