

International differences in CKD prevalence. A key public health and epidemiologic research issue

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Abstract

In this narrative review we studied the association of risk factors for CKD and CKD prevalence at an ecological level and describe potential reasons for international differences in estimated CKD prevalence across European countries. We found substantial variation in risk factors for CKD such as in the prevalence of diabetes mellitus, obesity, raised blood pressure, physical inactivity, and current smoking, and in salt intake per day. In general, the countries with a higher CKD prevalence also had a higher average score on CKD risk factors, and vice versa. There was no association between cardiovascular mortality rates and CKD prevalence. In countries with a high CKD prevalence the prevention of non-communicable diseases may be considered important and therefore all five national response systems (e.g. an operational national policy, strategy or action plan to reduce physical inactivity and/or promote physical activity) have been implemented. Furthermore, both the heterogeneity in study methods to assess CKD prevalence as well as the international differences in the implementation of lifestyle measures will contribute to the observed variation in CKD prevalence. A robust public health approach to reduce risk factors in order to prevent CKD and reduce CKD progression risk is needed and will have co-benefits for other non-communicable diseases.

Introduction

Individuals with CKD are at increased risk of all-cause and cardiovascular premature death, and may progress to end-stage renal disease (ESRD) [1-3]. The number of patients starting renal replacement therapy (RRT) due to ESRD varies from less than 30 to more than 200 people per million population across European countries and is much higher in most high-income countries compared to countries where access to health care is limited [4]. RRT has a significant impact on both individual patient quality of life [5, 6] and health system budgets [7, 8]. Therefore, where possible, public health initiatives are needed to prevent or delay the development of CKD (primary prevention) and its complications (secondary prevention), including ESRD.

The prevalence of risk factors for CKD, such as lifestyle factors, the difference in general population age distributions as well as differing cardiovascular mortality rates may partly explain international variation in CKD prevalence [9, 10]. Moreover, health policies addressing CKD prevention and treatment also vary widely across the region [11]. A better understanding of this complexity would guide the medical community and policy makers in targeting primary and secondary prevention efforts.

In this narrative review we will elaborate on the factors potentially underlying observed international differences in CKD prevalence in the elderly within Europe. We will do this by providing an overview of the prevalence of several CKD risk factors and cardiovascular mortality rates by country, and thereafter explore this in relation to the CKD prevalence focusing on countries with the highest and lowest CKD prevalence. In addition, we will discuss the heterogeneity of general population studies in their assessment of CKD which likely further contributes to the observed variation.

CKD prevalence in Europe

Figure 1 shows the age and sex adjusted prevalence of CKD stage 3-5 in the population aged 65-74 years in European countries and regions based on a study by Brück et al. on behalf of the European CKD Burden Consortium [12]. Figure 1 is adapted to include the CKD prevalence as reported by a recent published study based on the population-representative health survey for England [13]. The CKD prevalence varied from 4.1% (95% confidence interval (ci), 2.9-5.3) in the Swiss Bus Santé study to 25.5% (95% ci, 22.3-28.8) in the Northeast German SHIP study [12].

The comparability of CKD prevalence across countries and regions was increased by using the same definition of CKD, i.e. CKD stage 3-5 was defined as the presence of $\text{eGFR} < 60 \text{ ml/min}1.73\text{m}^2$ as calculated by the CKD-EPI equation, from a single serum creatinine measurement. Furthermore, the influence of different age and sex distributions was reduced through age and sex standardization to the European Union 27 population (with exception of the CKD prevalence reported for England). Moreover, as IDMS calibration standardization reduces the bias and improves the interlaboratory comparability [14], Figure 1 distinguishes between studies with IDMS and non-IDMS results.

Factors potentially underlying the international differences in CKD prevalence

The prevalence of risk factors for CKD, the cardiovascular mortality in the general population as well as public health policies may affect CKD prevalence. Figures 2a-2e show the prevalence of risk factors, i.e. diabetes mellitus [1], obesity [1], raised blood pressure [1], physical inactivity [15], current smoking [16] as well as salt intake [17]. Table 1 provides an overview of the estimated CKD stage 3-5 prevalence, together with an average score on the above mentioned risk factors for CKD in that particular country (see Table 1 for more details). In Table 1, we did not include countries with multiple estimations of CKD prevalence (France, Germany, Italy, and The Netherlands, see Figure 1). Moreover, England was not reported in Table 1 as an exact estimation of CKD stage 3-5 prevalence and a 95% confidence interval in age group 65-74 years was unavailable. Appendix Figure 1 shows the cardiovascular mortality rates, whereas Figure 3 presents the number of public health

policies targeting non-communicable diseases [18]. We used the most recent data available from various sources such as the World Health Organization (WHO) and World Bank (see figure legends for more details). Whenever possible, the estimates presented were age standardized. The categories presented in each Figure are based on quartiles. However, countries with a very similar prevalence of a risk factor were assigned to the same category.

Throughout this paper we will focus on those countries that have an estimation of CKD stage 3-5 prevalence in the age group 65-74 year as presented in Figure 1.

Diabetes mellitus

The prevalence of diabetes mellitus varied from 2,5% in the Republic of Moldova to 14,8% in Turkey (Figure 2a). Portugal had a relatively high prevalence of diabetes mellitus (9,6%), along with a high prevalence of CKD (Figure 1).

Body mass index

The percentage of obesity (body mass index ≥ 30 kg/m²) in the general population varied from 14,9% in Republic of Moldova to 29,5% in Turkey (Figure 2b). The United Kingdom ranked second with a prevalence of 28,1%. The low prevalence of diabetes mellitus (Figure 2a) in that country is therefore remarkable. Switzerland on the other hand had a relatively low prevalence of obesity (19,4%), together with a relatively low prevalence of CKD (Figure 1).

Raised blood pressure

The percentage of age standardized raised blood pressure varied from 15,2% in the United Kingdom to 31,7% in Estonia (Figure 2c). Although with some exceptions, the percentage of age standardized raised blood pressure was lower in countries in the Western part and higher in countries in the Eastern part of Europe.

Physical inactivity

The percentage of age standardized physical inactivity varied from 9,5% in Russia to 38,7% in Serbia (Figure 2d). After Serbia, the United Kingdom had the highest percentage of age standardized physical inactivity (37,3%), followed by Ireland (35,1%) and Portugal (34,9%).

Current smoking

The percentage of age standardized current smokers of any tobacco product varied substantially from 17,5 % in Iceland to 43,3% in Greece (Figure 2e). Behind Iceland and Denmark, The United Kingdom had the lowest percentage of age standardized current smokers (20,3%).

Salt intake

The mean daily salt intake in grams in the adult population was among the highest in Portugal (≥ 12 grams per day) and lowest in Germany (6-7 grams per day) (Figure 2f).

Table 1 provides an overview of estimated CKD stage 3-5 prevalence in the population aged 65-74 years of age, together with the average score on the risk factors for CKD (i.e. diabetes mellitus, obesity, raised blood pressure, physical inactivity, current smoking and salt intake) in that particular country. In general, countries with a higher CKD prevalence had a higher average score on the risk factors for CKD and vice versa. For example, Portugal had the highest estimate of CKD prevalence, and also the highest average score on CKD risk factors. On the other hand, Switzerland had the lowest estimate of CKD prevalence and the lowest average score on CKD risk factors.

Cardiovascular mortality in the general population

The age-standardized cardiovascular mortality per 100.000 deaths is lower in high-income European countries, and higher in low-income European countries (Appendix Figure 1). Cardiovascular mortality therefore shows the same pattern as all-cause mortality (http://www.who.int/healthinfo/mortality_data; data not shown). There was no association between cardiovascular mortality rates and CKD stage 3-5 prevalence across these countries.

Public health policy

The WHO Country Profiles 2014 lists national response systems which have been implemented to prevent and control non-communicable disease [18]. For the purpose of this review we used data on the implementation of the following national response systems per country, comprising an operational (multisectorial) national policy, strategy or action plan (1) that integrates several noncommunicable diseases and shared risk factors; (2) to reduce the harmful use of alcohol; (3) to reduce physical inactivity and/or promote physical activity; (4) to reduce the burden of tobacco use; or (5) to reduce unhealthy diet and/or promote healthy diets. Each country received a score, ranging from 0 to 5, based on the number of incorporated national response systems. A score of zero indicates that none of these five national response systems has been implemented in that particular country, and a score of five that all five national response systems have been implemented. The results are shown in Figure 3. In Portugal, a country with a high prevalence of CKD stage 3-5, the prevention of non-communicable diseases may be considered important and therefore all five national response systems may have been implemented.

Heterogeneity of studies on CKD prevalence

Study populations

Differences in CKD prevalence may be partly explained by heterogeneity in study populations. All studies assessing CKD prevalence presented in Figure 1 were designed to be representative of the respective regional or national general populations. Nevertheless, their sample selections varied considerably. Sample selection methods may have an effect on both the coverage of the population and the response rate. As a consequence, they may influence the representativeness of the sample [12]. Non-response analyses among several studies assessing CKD prevalence suggested that participants were equally healthy or healthier in comparison to non-participants [12]. Possibly, underrecruitment of patients with more advanced CKD provided a lower estimated CKD prevalence. Furthermore, as CKD prevalence may change over time [19, 20], some of the international differences in CKD prevalence may be explained by differences in the time period the study was performed.

Assessment of CKD prevalence

Differences in CKD prevalence may be due to the heterogeneity of methodology used in the included studies with regard to measurements of creatinine including differences in assays but also in handling and storage conditions [21, 22]. Moreover, regardless the use of IDMS standardization, we cannot rule out that some inter-laboratory variability still exists even within the IDMS studies [23].

Implementation of lifestyle measures

Previous studies have shown that by implementing life style measures, the prevalence of risk factors for CKD can be reduced at the general population level. For example, in several countries physical inactivity [24, 25], smoking [26], and salt intake [27] were all reduced after implementation of nationwide measures. However, great variation exists among European countries with regard to this implementation and this will likely have had an impact on the observed prevalence of risk factors of CKD.

First, the effect of lifestyle measures may vary across countries. For instance, the effect of raising taxes to reduce smoking differs across countries as smokers in high-income countries seem to be less responsive to price changes [28]. Nevertheless, the percentage of current smokers was relatively low in most high-income countries in comparison to low-income countries. Moreover, besides taxation measures, other effective tobacco use-reduction strategies may vary across countries, such as comprehensive bans on advertising and promotion of tobacco products, strong restrictions on smoking in work places and public spaces, education and counter-advertising campaigns and improved product warning labels [28]. It is possible that strategies addressing combinations of lifestyle measures may have a stronger effect than those addressing each lifestyle factor individually.

Furthermore, the time period in which life style measures were implemented may differ. For example, Finland began working on salt reduction as early as the 1970s, including public awareness campaigns [29]. In 1993, mandatory salt labelling was introduced, and products containing particularly high levels of salt were also required to bear warning labels. This was accompanied by the introduction of a “better choice” logo, supported by the Finnish Heart Association, which identified low-salt options. Daily salt intake in Finland dropped from approximately 12 g/day in the late 1970s to as low as 6.8 g/day among women already in 2002 [29]. In many European countries, however, national initiatives to reduce salt intake were not initiated before the new millennium [29]. For instance, in Portugal, the first national initiative to reduce salt was implemented in 2009 by setting a limit on the maximum amount of salt in bread ($\leq 1.4\text{g salt}/100\text{g}$). Additionally, in 2012 Portugal levied taxes on salt products [29]. Obviously, in Portugal, the effect of these implemented measures on salt intake may be seen only after 2009, which is much later than in Finland.

Also, one should take into account that the prevalence of risk factors of CKD already varied across countries before the implementation of lifestyle measures. For example, in the UK, the percentage of individuals fulfilling the criteria for sufficient physical activity was relatively low by the end of the previous century (i.e. 32% in men and 21% in women in 1997) [24], while in The Netherlands this percentage was relatively high in the beginning of this century (52% in 2001) [25]. Regardless the positive effect of the implementation of physical activity measures in the UK, the percentage of people fulfilling the criteria for physical activity was still low in this country in 2012 (43% in men and 32% in women) [24], whereas in The Netherlands the percentage of people who were physical active had further improved (62% in 2011) [25].

Noticeably, lowering one risk factor for CKD may also influence other risk factors for CKD or health outcomes. For instance, results of previously performed studies suggest that a decrease in physical inactivity is associated with a decrease in raised blood pressure and cardiovascular disease. Only few studies have described the impact of lifestyle improvements on kidney outcomes. Some evidence exists on the positive effect of salt reduction on both hypertension and proteinuria in people with CKD [30] and of smoking cessation on kidney function [31]. However, within these studies the outcomes were limited to proteinuria and kidney function instead of hard renal outcomes such as end stage renal disease [11].

Limitations

The association of risk factors for CKD with prevalence of CKD among European countries should be interpreted with caution.

As described above, the international comparison of prevalence of CKD may be hampered by heterogeneity of study methods. In addition, it is very likely that the violation of the chronicity criterion by using a single assessment of serum creatinine has led to a systematic overestimation of CKD prevalence in all countries and regions [32]. Furthermore, we were unable to include all European studies that published an estimation of CKD stage 3-5 prevalence, such as the one by Girndt et al., as they did not report the CKD prevalence for the age group 65-74 years [33].

Along the same lines, the international differences in the prevalence of *risk factors* for CKD (Figure 2) may also have been affected by sample selection. In addition, although several CKD risk factors are presented as age standardized values, for those risk factors that are non-age standardized (i.e. diabetes mellitus and salt intake) the differences in prevalence may be partly caused by differences in age distribution across the European countries. Moreover, it is unclear whether the assessment of risk factors for CKD was similar across countries or to what extent they may have suffered from measurement errors. For example, it is likely that a percentage of patients with type 2 diabetes mellitus remains undetected owing to a lack of overt symptoms. Also, lifestyle factors are usually assessed by self-reporting, such as physical inactivity, current smoking, and salt intake. Self-reported data are prone to validity problems, as individuals may over- or underreport, might be mistaken or may not remember the amount or frequency of the risk factor. It is also important to recognize that national response systems have been implemented to prevent and control several important non-communicable diseases and not only one non-communicable disease, CKD.

Within this narrative review we have discussed possible ecological associations (i.e. at a population level) between risk factors for CKD and prevalence of CKD. Also, the CKD stage 3-5 prevalence was estimated in the age group 65-74 year, whereas the estimation of the prevalence of lifestyle factors and cardiovascular mortality was assessed in the entire adult general population.

Additionally, one should bear in mind that, although the prevalence of risk factors of CKD and prevalence of CKD is often presented on a national level, it may vary by region [12]. It is possible that in some regions, like the South West of Germany and the North-West of France, a study on CKD prevalence was started due to the expected high CKD prevalence in that region, which may have resulted in selection bias (i.e. more studies with high CKD prevalence).

Finally, the figures in this paper presenting risk factors for CKD contain the most recent data available, although the current CKD prevalence is more likely to be caused by the prevalence of risk factors in previous years.

Conclusion

This narrative overview shows substantial variation among European countries in the prevalence of CKD, in the risk factors for CKD, in cardiovascular mortality rates, and in public health policies targeting non-communicable diseases. In general, the countries with a higher CKD prevalence also have a higher score on risk factors for CKD.

Whether individual countries and regions undertake public health policy and practice interventions based on such data or wait for studies providing more robust evidence of causality is beyond the remit of this paper to dictate. However, the general finding that higher prevalence of CKD risk factors may associated with higher prevalence of CKD suggests a need for action in tackling key risk factors.

Figure legends

Figure 1. The age and sex adjusted prevalence of CKD stage 3-5 in the general population 65- aged 74 years in Europe. * = Non-IDMS studies.

Figure 2a. Prevalence of diabetes mellitus among adults aged 20-79 years in 2015 (data from worldbank).

Figure 2b. Prevalence of age-standardized obesity (body mass index ≥ 30) among adults (18+ years) in 2014 (data from WHO).

Figure 2c. Prevalence of age-standardized raised blood pressure, among adults (18+ years) in 2010-2014 (data from WHO).

Figure 2d. Prevalence of age-standardized insufficient physical activity* among adults (18+) in 2010 (data from WHO). Insufficient physical activity was defined as less than 150 minutes of moderate-intensity physical activity per week or less than 75 minutes of vigorous-intensity physical activity per week or equivalent.

Figure 2e. Prevalence of age-standardized current smoking of any tobacco product among adults (18+ years) in 2013 (data from WHO).

Figure 2f. Estimates of salt intake among adults in gram per day. The year varies per country from 2000 to 2010 (data from Survey 2012 EU Salt Reduction Framework, EU commission).

Figure 3. National response systems to non-communicable diseases (data from WHO: non-communicable diseases Country profiles 2014).

Appendix:

Figure 1. Cardiovascular mortality, age-standardized per 100.000 deaths.

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Table 1. The age and sex adjusted prevalence of CKD stage 3-5 in the population 65-74 years by country (ordered from high to low) and the average score on risk factors for CKD.

Countries	CKD prevalence (95% confidence interval)*	Average score on risk factors for CKD**
Portugal	24.7 (21.1-28.4)	9.3
Spain	19.7 (15.8-23.6)	9.7
Ireland	19.5 (14.9-24.0)	8
Sweden	17.9 (15.6-20.3)	4.3
Poland	13.5 (11.8-15.2)	9.5
Finland	11.4 (8.6-14.2)	5.8
Norway	8.6 (8.0-8.2)	6.5
Switzerland	4.1 (2.9-5.3)	5.2

* For age and sex adjusted prevalence of CKD stage 3-5 in the population aged 65-74 years, see Brück et al.[12]. CKD prevalence was categorized in quartiles (see Figure1).

** The average score on risk factors for CKD was based on the prevalence of diabetes mellitus, obesity, raised blood pressure, physical inactivity, and current smoking and on salt intake (see Figure 2a-2f). The 13 countries with a known prevalence of CKD as shown in Figure 1 were ranked based on their prevalence of each risk factor (13 points for the country with the highest prevalence of that risk factor). Thereafter the scores were averaged by country and categorized in quartiles (red, orange, green and light green with red indicating the highest average risk score and light green the lowest average risk score. In Table 1, we did not include countries with multiple estimations of CKD prevalence (France, Germany, Italy, and The Netherlands, see Figure 1). Moreover, England was not reported in Table 1 as an exact estimation of CKD stage 3-5 prevalence and a 95% confidence interval in age group 65-74 years was unavailable.

Figure 1

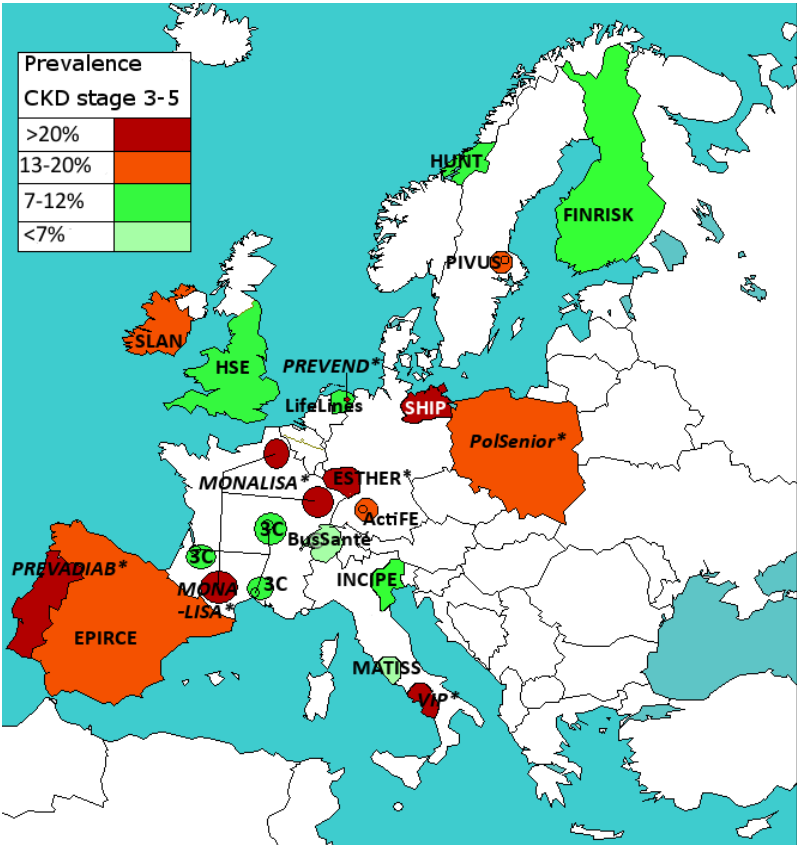


Figure 2a

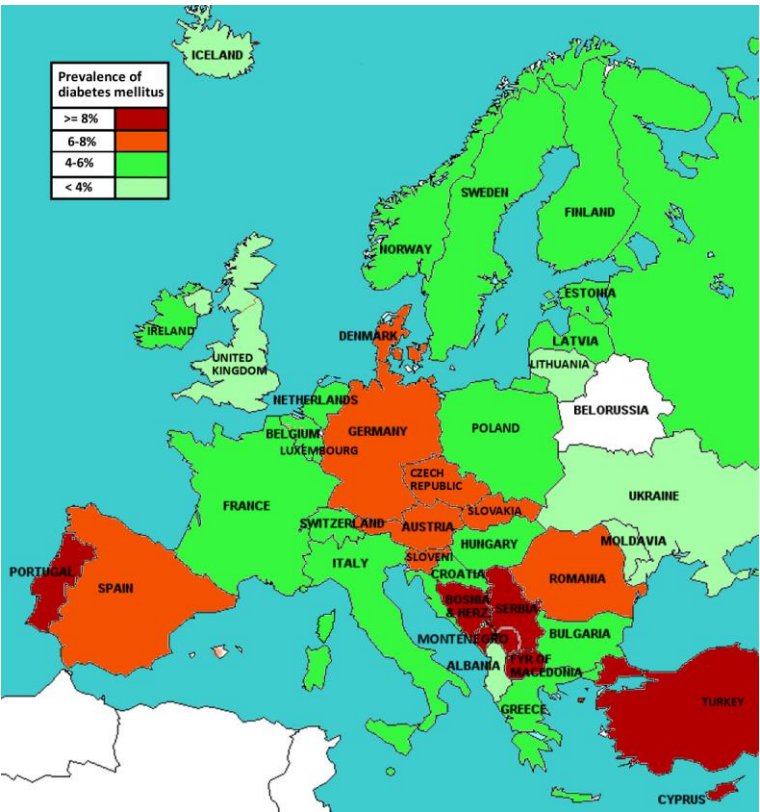


Figure 2b

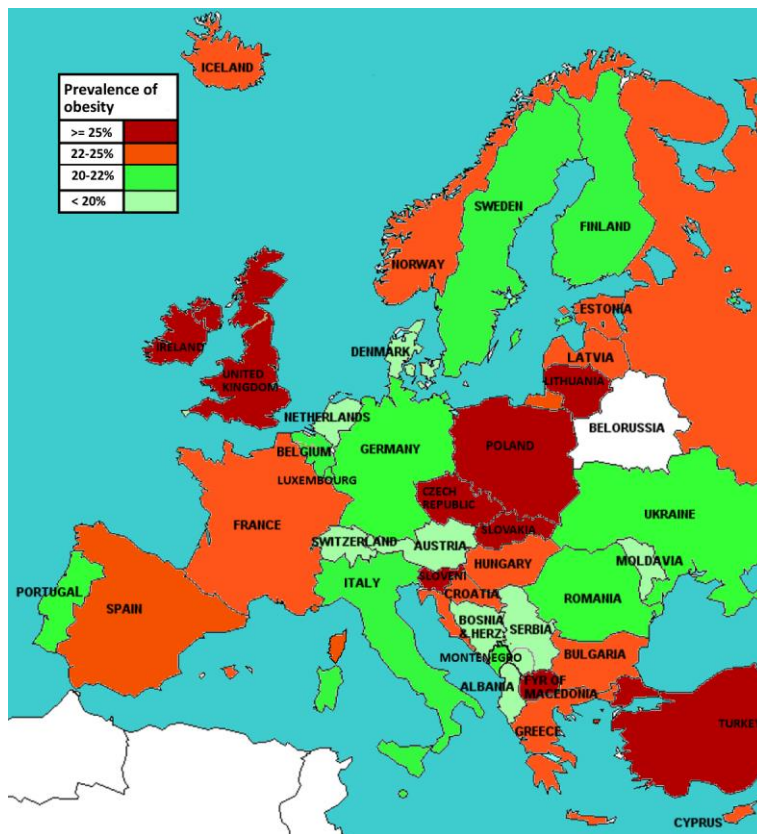


Figure 2c

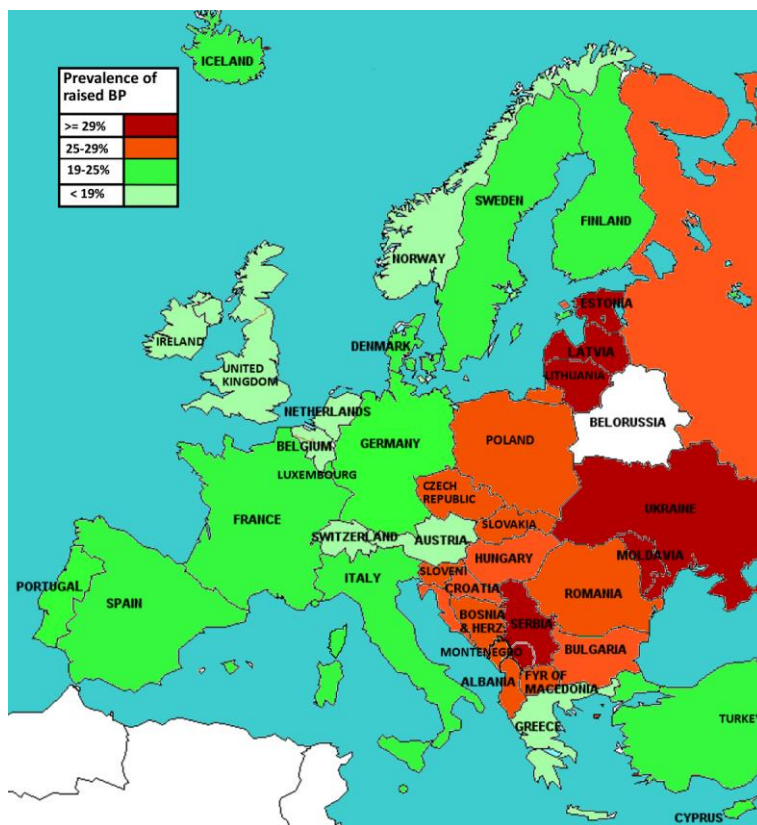


Figure 2d

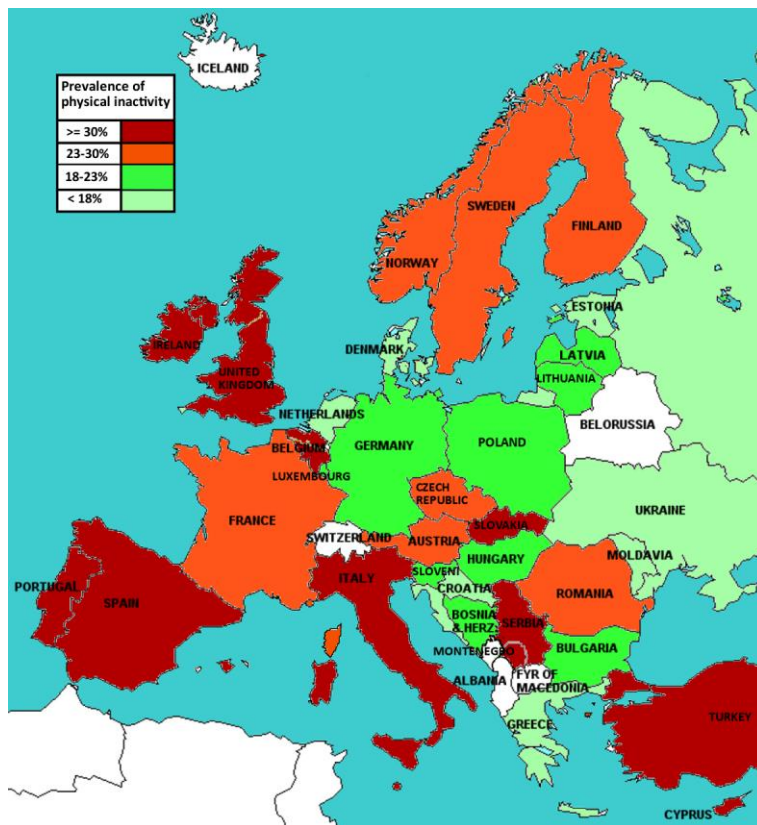


Figure 2e

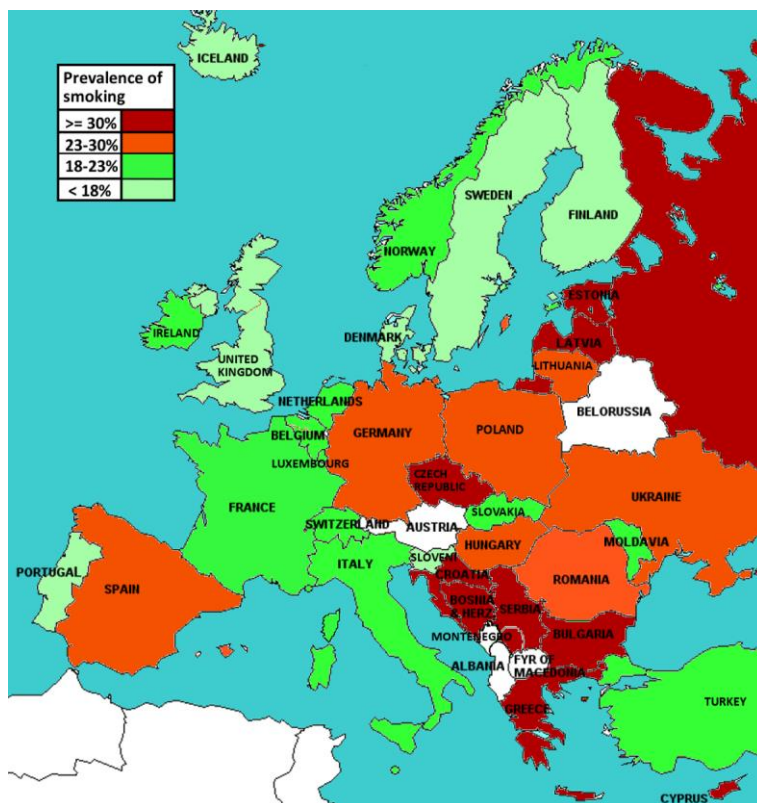


Figure 2f

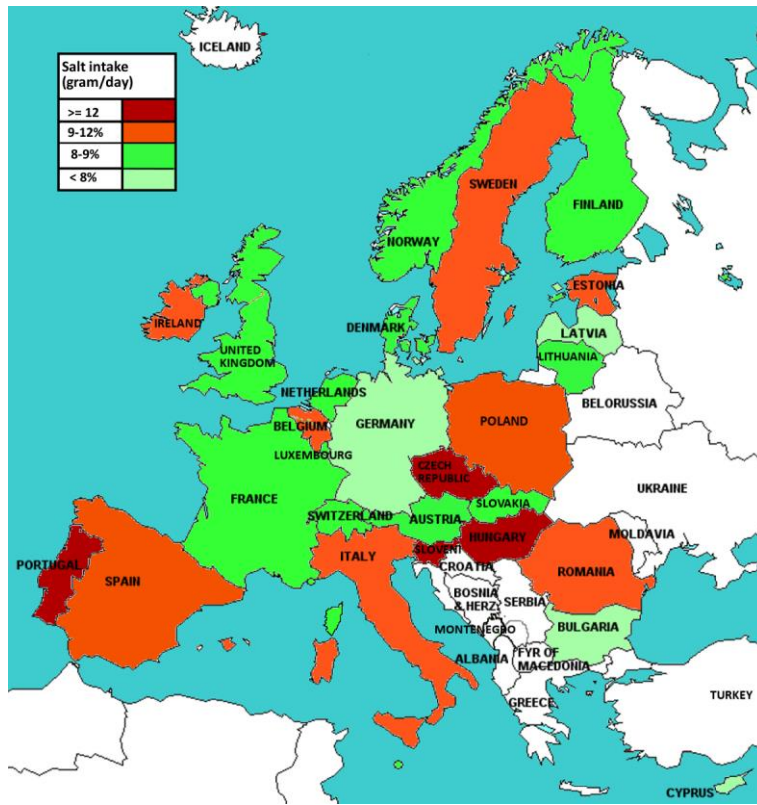


Figure 3

