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ORIGINAL ARTICLE

Regional differences in cardiovascular risk factor profile cannot fully explain differences in cardiovascular morbidity in the Netherlands: a comparison of two urban areas

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ABSTRACT

Background: Our objective was to investigate whether a region in the south of the Netherlands (Heerlen/Kerkrade) had a high burden of cardiovascular disease in comparison with a nearby region (Maastricht) and the average Dutch population, respectively. We also wanted to determine if there are interregional differences in cardiovascular risk factor profile.

Design: Cross-sectional study.

Methods: Data from a nationwide registry (CBS) were used to analyse cardiovascular mortality in the two regions and the average in the Netherlands. Data from a primary care morbidity registration network (RNH) were used to compare cardiovascular morbidity and cardiovascular risk factors in both regions. A standardisation procedure was carried out for age and sex. Data were analysed using logistic regression analyses.

Results: The overall cardiovascular mortality rate was higher in the Heerlen/Kerkrade region (7.8 ‰) compared with Maastricht (6.1‰, OR=1.3, 95% CI. 1.2-1.5) and the average in the Netherlands (5.7‰). Similarly, most cardiovascular morbidity rates for Heerlen/Kerkrade were more elevated compared with the RNH overall and with Maastricht. Prevalence rates of risk factors such as diabetes mellitus (7.2%, OR=1.5, 95% CI 1.3-1.7) and overweight (10.8%, OR= 2.0, 95% CI 1.8-2.2) were significantly higher in the Heerlen/Kerkrade region compared with Maastricht. There were no differences with regard to hypertension (15.2%, OR=1.0, 95% CI 0.9-1.1).

Conclusion: Heerlen/Kerkrade is indeed a region with a high burden of cardiovascular disease. Differences in morbidity between Heerlen/Kerkrade and Maastricht cannot be fully explained by differences in cardiovascular risk factor profile.

KEYWORDS

Cardiovascular diseases/mortality, Netherlands/epidemiology, morbidity/prevalence, risk factors

INTRODUCTION

Recently our group started the HIPPOCRATES project (Hypertension: Interaction and Prevalence of POlymorphisms related to Cardiovascular Risk and the Association to Treatment Efficacy Study).[1] The main objective of this study is implementation of genetic polymorphisms in the assessment of cardiovascular risk in primary care. This study utilises the population of a general practice centre located in the southeast of Limburg, i.e. an urbanised area around the cities of Heerlen and Kerkrade. From a population genetic point of view, this region is interesting in two aspects: (1) in unpublished Dutch reports a relatively high cardiovascular mortality

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has been described; (2) in and out migration figures are relatively low. Therefore, we were interested in the cardiovascular mortality of this region compared with the average in the Netherlands as well as with a region geographically nearby. Comparisons as these are usually limited to mortality data due to scarcity of national morbidity data. However, morbidity data give a better estimation of the prevalence of cardiovascular disease. Fortunately, sources for regional morbidity data are available from general practice registration networks.[2] Since in the Netherlands almost everyone is on the list of a general practitioner, morbidity registrations in these practices reflect the health status of a general population in a specific area. Our department coordinates such a primary care morbidity registration network.[2] Consequently, we had the opportunity to compare the morbidity figures of various regions. Moreover, we could explore the prevalence rates of some important cardiovascular risk factors also registered by this network (hypertension, diabetes mellitus, overweight and lipid disorders). Variation in risk factor profile might explain possible differences in cardiovascular mortality and morbidity profile between regions.[3,4] Comparing data on cardiovascular mortality and morbidity as well as risk factors could give insight into the specific cardiovascular profile of the study region. In this study the main question was whether the Heerlen/Kerkrade region does indeed have a high burden of cardiovascular disease compared with a nearby region (Maastricht) and the average of the Netherlands. A second question was whether there were interregional differences in cardiovascular risk factor profile.

Table 1 *Mortality and morbidity of categories of cardiovascular (CV) disease and risk factors studied and their ICD-10 and ICPC codes*

	Mortality (CBS database, ICD-10 codes)	Morbidity (RNH database, ICPC codes)
Disease category		
Ischaemic heart disease	I20 - I25	K74 - K76
Stroke	I60 - I69	K89 - K90
Other CV diseases:		
- Other heart disease	I00 - I09 I30 - I52	K70 - K73 K77 - K84
- Other vascular disease	I26 - I28 I80 - I89	I98 - I99 K93 - K99
- Peripheral arterial occlusive disease	I70 I73 - I74	K91 - K92
Risk factor category		
Hypertension	I10 - I13 I15	K85 - K87
Diabetes mellitus (I & II)	E10 - E14	T90
Overweight	E66	T82 - T83
Lipid disorders	E78	T93

CBS = Statistics Netherlands; RNH = Registration Network of General Practitioners.

METHODS

Cardiovascular mortality

From the official death certification data managed by Statistics Netherlands (CBS), the latest available mortality data (2000) were used on cardiovascular disease and risk factors for Heerlen/Kerkrade and Maastricht. Diagnoses were coded according to the International Classification of Diseases (ICD-10).[5] The validity of the death registry is generally considered sufficiently good for epidemiological use.[6,7] The disease categories studied are presented in *table 1*.

Cardiovascular morbidity

Cardiovascular morbidity rates were retrieved from the Registration Network of General Practitioners (RegistratieNet Huisartspraktijken, RNH). This is a continuous and computerised database in which 63 general practitioners (GPs) working in 22 different practices in the south of the Netherlands participate. All relevant health problems are registered. A health problem is defined as 'anything that has required, does or may require healthcare management and has affected or could significantly affect a person's physical or emotional well-being'.[8] Health problems are only coded by the GPs if they are permanent (no recovery expected), chronic (duration longer than six months), recurrent (more than three recurrences within six months), or when they have lasting consequences for the functional status or prognosis of the patient. Problems are coded according to the International Classification of Primary Care (ICPC) using the criteria of the International Classification of Health Problems in Primary Care for diagnoses.[9,10] The registered data are continuously updated and historically cumulated for each patient. Population membership only ends by migration or death. The quality of the data is ensured by instruction and training sessions, regional consensus groups, quality control experiments and by an automated thesaurus and automated checking for erroneous or missing entries.[11]

For this study, data from five general practices (n=10,587) in Heerlen/Kerkrade (index population) and from three general practices (n=8742) in Maastricht (control population) were used. For both regions and the RNH overall (n=56,976) prevalence rates were calculated. We compared the prevalence rates of Heerlen/Kerkrade with Maastricht. Age and sex distribution of the total RNH dataset was reported to be similar to that of the Netherlands.[8] Comparison of the

age and sex distribution of the total RNH dataset (2001) with the Netherlands (2001) still appeared to be the same. Age- and sex-specific data were drawn from the latest RNH dataset available (1 July 2001). The disease categories studied are presented in *table 1*.

Cardiovascular risk factors

Prevalence rates of cardiovascular risk factors were also retrieved from the eight general practices in Heerlen/ Kerkrade and Maastricht. Age- and sex-specific data were drawn from the latest RNH dataset available (1 July 2001). The risk factors studied are also presented in *table 1*.

Statistical analysis

To compare the prevalence of cardiovascular mortality and morbidity between both regions (Heerlen/Kerkrade vs Maastricht), a standardisation procedure was carried out for sex and age, in which the standard population was the population of all RNH practices. To determine whether the observed differences between both regions were statistically significant, logistic regression analyses were performed, using the statistical software programme SPSS 9.0 for Windows. In the analyses regarding mortality, the dependent variable was presence or absence of a specific cause or causes of death; in those regarding morbidity and risk factors, the dependent variable was presence or absence of the disease category or risk factor. The independent variable was 'region' (Heerlen/Kerkrade *vs* Maastricht) with potential confounders sex and age distribution. First, all variables were entered in the model, followed by all possible interaction terms (method: enter). The model was then further fitted, based on the statistical significance of the various interaction terms (region times age, region times sex, sex times age) according to the likelihood ratio test. In all analyses, age was entered as a categorical variable since this improved the Hosmer-Lemeshow goodness-of-fit tests considerably.[12]

RESULTS

General characteristics

The general characteristics of the study populations are summarised in *table 2*. With regard to mortality data (CBS), there were hardly any differences in age distribution between both regions. With regard to morbidity data (RNH), the population of Heerlen/ Kerkrade was slightly older than that of Maastricht. Both CBS and RNH populations contained slightly more females than males. Overall, both study populations were very comparable regarding to age and sex.

Cardiovascular mortality

Mortality figures of some cardiovascular diseases or risk factors were so small that no meaningful analyses could be performed. This was the case for 'other vascular disease' and 'peripheral arterial occlusive disease' and for all the risk factors. *Table 3* shows standardised mortality rates of cardiovascular diseases for both regions and the average in the Netherlands. The overall trend for all categories was that mortality rates were higher in Heerlen/Kerkrade compared with Maastricht. The most distinct difference was found for 'ischaemic heart disease'. *Figure 1* shows the age-specific mortality rates for the two regions. For every age group, the mortality rate was higher in Heerlen/Kerkrade compared with Maastricht. However, the pattern of the mortality rates was comparable in the two regions.

Table 2 *Sex and age distribution of the study populations for mortality and morbidity*

	Mortality analyses* %			Morbidity analyses** %		
Characteristic	The Netherlands (n=8,544,381)	Maastricht (n=67,975)	Heerlen/Kerkrade (n=87,444)	RNH (n=56,976)	Maastricht (n=8742)	Heerlen/Kerkrade (n=10,587)
Sex						
Male	48.2	47.3	47.7	48.1	46.9	48.3
Female	51.8	52.7	52.3	51.9	53.1	51.7
Age (years)						
35-44	29.6	27.2	27.8	27.5	28.8	26.5
45-54	26.7	25.4	25.1	26.4	23.7	25.9
55-64	18.5	18.9	18.9	19.6	18.7	19.5
65-74	14.0	15.8	16.0	15.4	16.4	15.9
75-84	8.6	9.8	9.8	9.0	9.6	10.0
≥85	2.6	2.8	2.4	2.1	2.8	2.1

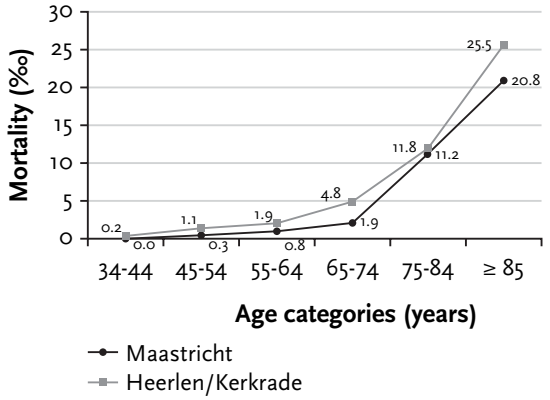
*Based on Statistics Netherlands (CBS) database 2000; **based on Registration Network of Family Practitioners (RNH) database 2001.

Table 3 *Standardised mortality rates of cardiovascular (CV) disease for two urban regions (n=155,419) and the Netherlands (n=8,544,381)*

	The Netherlands (‰)	Maastricht (‰)	Heerlen/Kerkrade (‰)	Significance of the variable 'region'
Mortality category				
Ischaemic heart disease	2.0	2.2	3.1	OR=1.4 (1.2-1.7)** †
Stroke	1.4	1.5	1.8	OR=1.2 (0.95-1.5)** †
Other CV disease	-*	2.4	2.9	OR=1.2 (1.03-1.5)** †
Other heart disease	-*	1.6	2.2	OR=1.3 (1.07-1.7)** †
Overall CV diseases	5.7	6.1	7.8	OR=1.3 (1.2-1.5)** †

*No comparable data available; **Heerlen/Kerkrade *vs* Maastricht; † 95% confidence interval.

Figure 1 *Age-specific mortality rates for ischaemic heart disease (CBS mortality data)*



Logistic regression analyses confirmed the statistical significance of the differences between the two regions. The variable 'region' had an independent association with mortality in the categories 'ischaemic heart disease' (OR=1.4 (1.2-1.7)), 'other heart disease and vascular disease' (OR=1.2 (1.03-1.5)), 'other heart disease' (OR=1.3 (1.07-1.7)). No independent association was observed for the mortality category 'stroke'.

Cardiovascular morbidity

In *table 4* standardised prevalence rates of cardiovascular morbidity are presented for both regions. Overall, the Heerlen/Kerkrade region consistently showed a higher prevalence of cardiovascular morbidity in comparison with Maastricht. The most distinct differences between the regions were found with respect to 'ischaemic heart

Table 4 *Standardised prevalence rates of cardiovascular (CV) disease and risk factors for two urban regions (n=19,329) and the RNH overall (n=56,976)*

	RNH (%)	Maastricht (%)	Heerlen/Kerkrade (%)	Significance of the variable 'region'
CV disease category				
Ischaemic heart disease	8.5	7.8	9.6	In interaction with age
Stroke	3.7	3.9	4.0	OR=1.0(0.9-1.2)** †
Other CV diseases:	19.6	20.1	22.3	OR=1.2 (1.1-1.3)** †
- Other heart disease	7.4	7.6	7.5	OR=1.0 (0.9-1.1)** †
- Other vascular disease	11.6	12.4	14.1	OR=1.2 (1.1-1.3)** †
- Peripheral arterial occlusive disease	3.2	2.8	3.9	OR=1.4(1.2-1.7)** †
Overall CV diseases	25.8	25.9	28.9	OR=1.2 (1.1-1.3)** †
CV risk factor category				
Hypertension	14.6	15.3	15.2	OR=1.0 (0.9-1.1)** †
Diabetes mellitus (I & II)	6.3	5.0	7.2	OR=1.5 (1.3-1.7)** †
Overweight*	7.5	5.8	10.8	OR=2.0 (1.8-2.2)** †
Lipid disorders	6.4	5.5	8.0	In interaction with age and sex

*BMI ≥25; **95% confidence interval; † Heerlen/Kerkrade *vs* Maastricht; RNH = Registration Network of Family Practitioners.

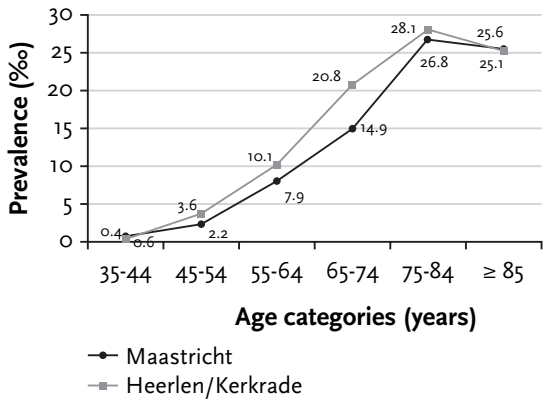
disease' and 'other heart and vascular diseases', in which the main contribution came from 'other vascular disease'. *Figure 2* shows the trend of the prevalence rates of ischaemic heart disease in both regions. The prevalence rate of Heerlen/Kerkrade for every age group was consistently above Maastricht, except for the youngest and the oldest age category. For all other cardiovascular morbidity categories, the prevalence rate of Heerlen/Kerkrade lay consistently above Maastricht. Comparatively, the relative risk was the highest for peripheral arterial occlusive disease. Logistic regression analyses confirmed the statistical significance of the differences between both regions in most cases. The variable 'region' had an independent association with morbidity in the categories 'other heart and vascular disease' (OR=1.2 (1.1-1.3)), 'other vascular disease' (OR=1.2 (1.1-1.3)) and 'peripheral arterial occlusive disease' (OR=1.4 (1.2-1.7)). It was significant in interaction with age for 'ischaemic heart disease', indicating that in all age categories the prevalence of ischaemic heart disease was higher in Heerlen/Kerkrade than in Maastricht, except for the age category 35 to 44 and ≥85. Differences in prevalence rates for stroke and 'other heart disease' were small, which was confirmed by the results of the logistic regression analysis (*table 4*).

Cardiovascular risk factors

In the second part of *table 4* standardised prevalence rates of available cardiovascular risk factors are presented for both regions. The prevalence of the cardiovascular risk factors studied was higher in Heerlen/Kerkrade compared with Maastricht. This holds especially for 'diabetes mellitus', 'overweight' and 'lipid disorders'. Regarding 'hypertension', the difference was small.

Logistic regression analyses confirmed the statistical significance of the differences between both regions in most cases. With respect to the cardiovascular risk factors studied, the variable 'region' had an independent association with 'diabetes mellitus' (OR=1.5 (1.3-1.7)) and with 'overweight' (OR=2.0 (1.8-2.2)). For 'lipid disorders', it was significant in interaction with age and sex, indicating that if age rises, more males develop lipid disorders in the region Heerlen/Kerkrade than in Maastricht. The difference in prevalence rates of hypertension was small, which was confirmed by the results of the logistic regression analysis.

Figure 2 *Age-specific prevalance rates for ischaemic heart disease (morbidity data from the RNH database)*



DISCUSSION

The present study showed that cardiovascular mortality rates were higher in the region Heerlen/Kerkrade compared with both the average in the Netherlands and in Maastricht in particular. Similarly, most cardiovascular morbidity rates for Heerlen/Kerkrade were more elevated compared with the RNH overall and more specifically with Maastricht. In accordance with these results prevalence rates of cardiovascular risk factors – in particular diabetes mellitus, overweight and lipid disorders, but not hypertension – were significantly higher in the Heerlen/Kerkrade region.

Before discussing possible explanations and the relevance and implications of these findings, it is important to discuss in short the validity of the registration systems used. In the case of mortality data (CBS), validity depends on the accuracy of the registration of the primary cause of death. Several studies have assessed the validity of the Dutch mortality registration and confirmed the completeness of this registration.[6,7,13] However, discrepancies have been found between the judgement of physicians and subsequent findings at autopsy and between physicians coding identical cases for research purposes.[6,14] Using broad categories, as was done in this study, is known to lead to fewer discrepancies than analysing single disorders.[14,15] We have no reason to assume there are regional differences with regard to registration of death certificates by doctors. Regarding data on morbidity and risk factors (RNH), validity depends on the accuracy of the registration of the diagnostic problems by the general practitioners involved. The quality is ascertained by instruction and training sessions, regional consensus groups, quality control experiments and by an automated thesaurus and automated checking for erroneous or missing entries.[8] There were no differences between the selected general practices in both regions with regard to participation in cardiovascular research projects over the last 13 years.

Our results demonstrate that Heerlen/Kerkrade is indeed a region with a high burden of cardiovascular disease, in comparison with Maastricht and the average in the

Netherlands. Given the fact that five general practices in Heerlen/Kerkrade are included in the RNH overall, the estimates of the prevalence rates for cardiovascular morbidity in the RNH overall are probably higher than the average in the Netherlands. Consequently, average cardiovascular morbidity figures for the Netherlands will probably be lower than presented here.

Data from the Framingham study show that important cardiovascular risk factors such as hypertension, diabetes mellitus, overweight and lipid disorders have a mutual amplifying effect.[16] Our results show a relatively high prevalence of diabetes mellitus, overweight and lipid disorders in Heerlen/Kerkrade and this will contribute to a higher prevalence rate of cardiovascular mortality and morbidity. However, the prevalence rates for hypertension did not differ in the two regions. A Dutch study using CBS data for the period 1950 to 1984 suggested that excess cardiovascular mortality appearing in the south of the Netherlands could be explained by Roman Catholic lifestyle and relatively lower income.[17] Unpublished reports for the Heerlen/Kerkrade region and Maastricht on these cardiovascular risk factors as well as for alcohol use, showed inconsistent differences. No data were available on risk factors such as elevated homocysteine levels and unfavourable nutrition patterns.[18-21]
Our results are consistent with the complex relationship between cardiovascular morbidity and multiple cardiovascular risk factors.[22] However, the excess risk observed in the Heerlen/Kerkrade region as compared with the Maastricht region can not be fully explained on the basis of a higher prevalence of risk factors. For instance, in subjects from Heerlen/Kerkrade with hypertension, the risk of coronary complications was substantially greater than that predicted from placebo-treated patient populations in major clinical trials.[23] In the pathogenesis of cardiovascular disease many factors, including genetic and environmental factors, play a role.[24,25] Genetic factors that modulate the individual susceptibility to cardiovascular disease are common, functionally different types of genes (polymorphisms).[26-29] These polymorphisms generally have a modest effect at an individual level, but because of their high frequency in the population can be associated with a high attributable risk.[30] Environmental factors can reveal or facilitate the phenotypic expression of such susceptibility genes. There is now accumulating evidence that most of the susceptibility genes for common diseases do not have a primary aetiological role in predisposition to disease, but rather act as response modifiers to exogenous factors such as stress, environment, disease, and drug intake.[30] A better characterisation of the interactions between environmental and genetic factors constitutes a key issue in the understanding of the pathogenesis of cardiovascular disease.[31-33] Therefore it is important to study all these factors on an individual level.

CONCLUSION

The Heerlen/Kerkrade region is indeed a region with a high burden of cardiovascular disease. However, the differences in morbidity between Heerlen/Kerkrade and Maastricht cannot be fully explained by differences in cardiovascular risk factor profile. Therefore a better characterisation of the interactions between environmental and genetic factors is important in cardiovascular research in the Heerlen/Kerkrade region.

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