Bulletin of the World Health Organization 57 (2): 291-299 (1979)

Myocardial infarction and water hardness in the WHO myocardial infarction registry network

R. MASIRONI,[1] Z. PIŠA,[2] & D. CLAYTON[3]

The negative association between water hardness and cardiovascular disease found by several authors in different countries has also been found in the present investigation. All cases of myocardial infarction were registered in a standardized way at 15 WHO Collaborating Centres in Europe; information on the hardness of drinking water used by the population studied was also collected. Higher rates of myocardial infarction were usually found in towns served by softer water.

Since the initial report by Kobayashi (*1*) in 1957 on the relationship between the chemical composition of river water and death rates from cerebral haemorrhage in Japan, several articles have been published showing inverse relationships between the hardness of local water supplies and mortality rates from cardiovascular diseases in various countries. Although it has not yet been possible to establish any relationship between cause and effect, the existence of an association with mortality cannot be dismissed. This was also the conclusion of an international group of experts who met in 1975 under the auspices of the Commission of the European Communities (*2*).

The negative association is more evident in studies covering very wide geographical areas and involving large numers of people; smaller studies comparing, for instance, districts within the same town or counties within the same state often do not reveal any association. Studies in such small areas are likely to be influenced by the small population size and by such factors as the use of water softeners in the home. Neri & Johansen (*3*) have recently reviewed the abundant literature on this subject.

Taking advantage of the WHO Myocardial Infarction Community Registers in 17 European towns and cities, the present investigation was set up to ascertain whether the negative association between the harness of municipal water and cardiovascular pathology was present throughout part of Europe, as it is in Canada, the United Kingdom, the United States of America, and other countries. The present study was undertaken specifically in response to the suggestions of a group of investigators meeting under the auspices of WHO in November 1974,[a] who considered that it would provide a unique opportunity for the study of sudden death and incidence of ischaemic heart disease (IHD) in relation to water quality.

MATERIALS AND METHODS

Disease frequency

Detailed information on the incidence of acute myocardial infarction was obtained from collaborating hospitals located in 17 European towns and cities, namely Berlin, Boden, Bucharest, Budapest, Dublin, Gothenburg, Heidelberg, Helsinki, Innsbruck, Kaunas, London, Lublin, Nijmegen, Prague, Sofia, Tampere, and Warsaw. These data were collected in a standardized way and have been reported in a WHO publication (*4*), which also contains all the details on the rationale, methodolo-

[1] Scientist, Cardiovascular Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

[2] Chief, Cardiovascular Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

[3] Senior Lecturer in Medical Statistics, Department of Community Health, Leicester University, Leicester, England.

[a] Report of second meeting of investigators on trace elements in relation to cardiovascular diseases. WHO unpublished document CVD/73.4 (1973).

gy, and operation of these registers. The population covered by the study was all persons aged 20-64 years of age, giving a total of 3 570 150 subjects.

The methodology used in the present register allows the calculation of the following measures of disease frequency:

Attack rate, i.e., the rate of occurrence of heart attacks in the defined community. It should be noted that any individual could, and many did, suffer more than one attack during the period of study.

Table 1. Age standardization of attack and incidence rates

Age group (years)	Males	Females	Both sexes
45–49	0.145	0.145	0.290
50–54	0.112	0.112	0.224
55–59	0.126	0.126	0.252
60–64	0.117	0.117	0.234
45–64	0.5	0.5	1.0

Incidence rate, i.e., the rate of occurrence of *first* attacks in the community. Technically, incidence rates cannot be calculated from register data since the appropriate denominator (the number of individuals at risk who have not suffered previous attacks) is unknown. In the age group considered, however, use of the total population as the denominator should be acceptable.

Age-specific attack and incidence rates have been reported for each collaborating centre (*4*) but we chose not to use age-specific rates as the data are too sparse to provide accurate rates within 5-year age groups. Age-standardization of results was therefore chosen. The form of the tabulations available necessitated the use of direct standardized rates, but in view of the inefficiency of this method of standardization when dealing with very sparse data, the younger age groups (<45 years) had to be omitted and the analysis performed on rates standardized within the 45–64-year age group. Rates were standardized for the population structure shown in Table 1, both sexes being assigned the overall age structure of the total population served by the registers. The standardized rates used are shown in Table 2.

Table 2. Standardized attack and incidence rates per 1000 persons per year aged 45–64 years

City	Weighted water hardness (mg/l $CaCO_3$)	Age-standardized attack rate		Age-standardized incidence rate		Age and sex standardized:	
		M	F	M	F	attack rate	incidence rate
Boden	32	9.93	3.67	7.01	2.54	6.80	4.78
Tampere	44	14.99	2.95	8.98	1.85	8.97	5.42
Gothenburg	45	6.48	1.52	4.02	0.94	4.00	2.48
Dublin	46	11.56	3.27	8.01	2.29	7.42	5.15
Helsinki	91	17.75	4.13	10.31	2.71	10.94	6.51
Prague	116	8.45	1.56	5.31	1.10	5.01	3.21
Bucharest	146	3.72	1.17	2.45	0.83	2.45	1.64
Innsbruck	147	6.56	1.35	3.05	0.92	3.96	1.99
Nijmegen	159	11.45	2.35	7.84	1.82	6.90	4.83
Warsaw	221	7.13	2.37	4.94	1.71	4.75	3.33
Budapest	273	6.79	2.02	4.77	1.61	4.41	3.19
London	291	9.62	2.77	5.84	1.91	6.20	3.88
Berlin	300	6.26	2.33	2.75	1.44	4.30	2.10
Lublin	336	6.10	1.31	4.14	0.86	3.71	2.50
Heidelberg	354	6.09	0.89	4.07	0.67	3.49	2.37

Water hardness

The principal investigators of the collaborating centres were asked to supply WHO with information on the average hardness of the drinking water. Since such information could not be obtained from two of the centres, the calculations have been made relative to only fifteen of the centres. Some of the centres also provided additional information on water composition, such as pH, concentrations of calcium, magnesium, sodium, and potassium, and occasional trace element analyses. However, this kind of information was too sparse to be of any use statistically.

Of the fifteen centres that replied to the enquiries, not one represented a community that was supplied with water from only one source. A major problem, therefore, was how best to combine information concerning various sources to achieve an average value for the whole community. In most cases, where sources of markedly different levels of hardness were involved, the principal investigator supplied approximate data on the size of the population receiving water from each source. These populations were used as weights in calculating an average value. Such information was not available for Innsbruck, but we were supplied with estimated volumes produced by each source and these were used as weights. (This involves some risk in that some sources can supply large volumes for industrial use, but this is probably not a problem in Innsbruck.) In most communities, the various sources did not differ in hardness sufficiently for weighting to have very much effect and a straightforward average value was used. In Heidelberg, of the twelve water supplies, only one had water of a much lower harness than the others, and it served only a few thousand people. Hardness values for Heidelberg were weighted both by the populations served and by the approximate sizes of town districts with a given water hardness. Table 2 shows the water hardness values.

Water hardness data thus obtained were correlated with sex and with attack and incidence rates by least-squares regression analysis. Both variables (disease rate and water hardness) were log-transformed for better clarity of graphic display.

RESULTS

Association between disease frequency and water hardness

Table 3 shows the product–moment correlation coefficients, together with the parameters of the fitted regression lines. Since the regression slopes were very similar for both sexes, the average of the male and female rates was taken to give age- and sex-standardized attack and incidence rates (Fig. 1 and 2). The associations were significant at the 0.1 % level.

Table 3. Regression lines: log (rate) versus log (water hardness)

	Correlation	Slope	Intercept.	Significance
Attacks, males[a]	−0.428	−0.211	1.360	N.S.
Attacks, females[a]	−0.468	−0.251	0.843	$P<0.10$
Incidence, males[a]	−0.442	−0.234	1.203	$P<0.10$
Incidence, females[a]	−0.397	−0.211	0.597	N.S.
Attacks[b]	−0.477	−0.228	1.195	$P<0.10$
Incidence[b]	−0.460	−0.228	0.999	$P<0.10$

[a] Age standardized, 45–64 years.
[b] Age & sex standardized, 45–64 years.

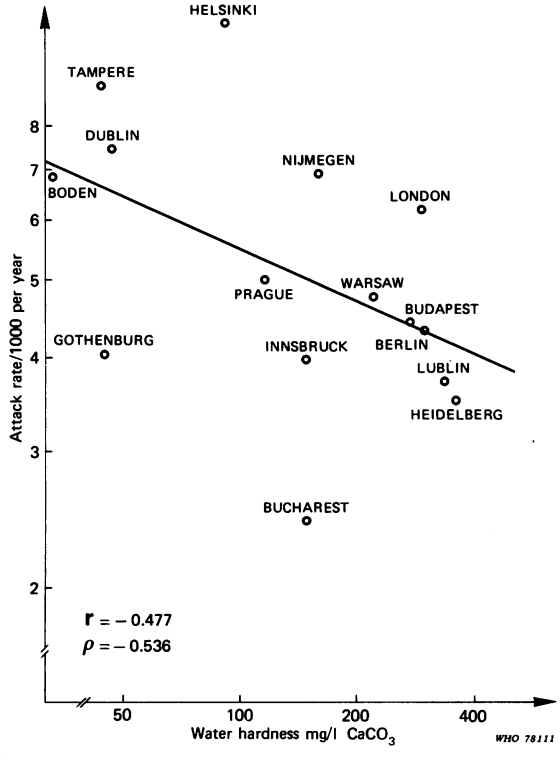

Fig. 1. Age- and sex-standardized attack rates in persons aged 45-64 years.

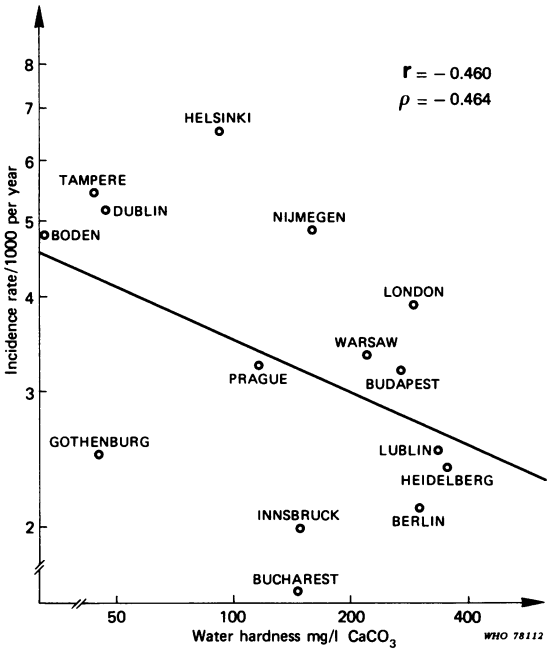

Fig. 2. Age- and sex-standardized incidence rates in persons aged 45-64 years.

To check further the significance of the observed association, a rank-correlation analysis (Spearman's ϱ) was also performed. With this analysis, the association between water hardness and attack rate was significant at the 5% level.

From these results, it appears that there is an inverse association between the occurrence of myocardial infarction in these communities and the hardness of their water supplies.

Latitude and temperature

There was a strong relationship between the frequency of myocardial infarction and latitude. Both attack and incidence rates were higher, and water softer, at more northerly latitudes.

Fig. 3 shows the relationship between attack rate and latitude; the fitted regression relationship was consistent with the attack rate doubling for each 15° of latitude. Fig. 3 also indicates the water hardness for the 15 communities studied and shows that the associations with latitude and with hardness were the same. Towns with high attack rates for their latitude (above the regression line) differed little in water hardness from towns with low attack rates for their latitude (below the regression line). The incidence of myocardial infarction in most of the populations studied appeared to be higher than average from February to June and lower from July to October. An investigation was made into the likelihood of the latitude effect and the seasonal variation in incidence of myocardial infarction having a common cause. The results are shown in Table 4, where the degree of seasonal swing in incidence rate is related to latitude. The association observed was statistically significant but was not in the expected direction, the more northerly towns with the highest incidence (and attack) rates having the *smallest* seasonal swings in such rates. Indeed, the three cities above latitude 60° north were among those with the smallest seasonal swings in incidence. A preliminary attempt to correlate yearly mean minimum temperatures for the areas under study (as taken from atlases and statistical yearbooks) revealed a significant negative trend ($r = -0.57$) with latitude and a weak

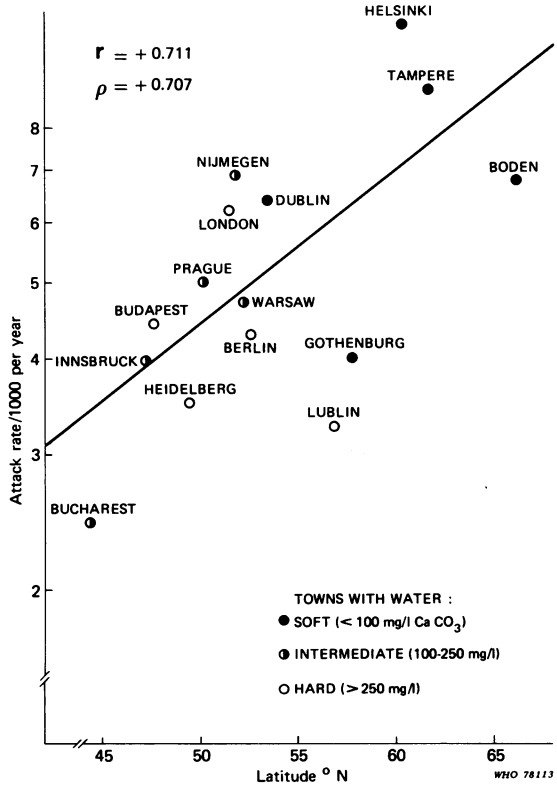

Fig. 3. Age- and sex-standardized attack rates in relation to latitude.

Table 4. Seasonal variations in myocardial infarction incidence rates in relation to latitude[a]

City	Ratio[b]	Incidence[c]	(Rank)	Latitude (degrees north)	(Rank)
Tampere	0.84	5.42	(13)	61.5	(13)
Lublin	1.02	2.50	(3)	51.2	(6)
Helsinki	1.07	6.51	(14)	60.3	(12)
Boden	1.10	4.78	(10)	65.9	(14)
Heidelberg	1.19	2.37	(2)	49.4	(4)
Nijmegen	1.23	4.83	(11)	51.8	(8)
Innsbruck	1.27	1.99	(4)	47.2	(2)
Prague	1.33	3.21	(8)	50.1	(5)
Budapest	1.34	3.19	(6)	47.5	(3)
London	1.34	3.88	(9)	51.5	(7)
Warsaw	1.52	3.33	(7)	52.1	(9)
Gothenburg	1.59	2.48	(5)	57.7	(11)
Dublin	1.59	5.15	(12)	53.4	(10)
Bucharest	2.98	1.64	(1)	44.4	(1)
Spearman's ϱ			−0.297		−0.336

[a] From *Myocardial Infarction Community Registers*. Copenhagen, WHO Regional Office for Europe, 1976, Table 66 and Fig. 27.

[b] Ratio of daily incidence in high-incidence months to daily incidence in low-incidence months (seasonal swing).

[c] Age and sex standardized.

negative trend ($r = -0.33$) with attack rate (Table 5). The weak positive ($r = +0.44$) correlation between temperature and water hardness confirmed the finding that the more northerly areas usually have lower temperatures and also softer water. These associations are similar to those found in the United Kingdom by Crawford et al. (*6*, *7*), who reported positive correlations between death rates from cardiovascular diseases and latitude ($r = +0.27$) and negative ones between water hardness and latitude ($r = -0.37$) and, of course, between death rates and water hardness ($r = -0.61$).

Diet

Previous studies have clearly shown relationships between aspects of the diets of various European countries and death rates from IHD (*8*). In particular, the percentage of calories obtained from fats has been implicated. By applying national dietary data to the subjects in the present study, a moderately strong ($r = +0.55$) positive correlation was obtained between fat consumption (g/day/person) and attack rate (Table 5). A positive correlation ($r = +0.50$) was also found between fat consumption and latitude, but not water hardness ($r = -0.11$). A weak correlation was found between fat consumption and mean lowest yearly temperatures ($r = +0.21$).

Table 5a. Correlation between myocardial infarction rates, geographical parameters, and fat consumption

City	Myocardial infarction attack rate in males 50–54 years of age	Latitude (degrees north)	Water hardness (mg/l $CaCO_3$)	Mean lowest yearly temperature		Consumption of animal fat (g/day/person)
				°C	K	
Boden	9.0	65.9	33	−8.6	264.5	94.9
Tampere	13.3	61.5	62	−7.8	265.3	101.5
Helsinki	14.5	60.3	93	−6.1	260.9	101.5
Gothenburg	5.5	57.7	45	−4.3	268.8	94.9
Berlin	3.6	52.5	313	−0.7	272.4	101.8
Dublin	10.9	52.4	64	+4.0	277.1	115.3
Warsaw	5.9	52.2	220	−4.9	268.2	73.1
Nijmegen	9.9	51.8	153	+2.2	275.3	99.7
London	8.0	51.5	291	+5.0	278.1	116.3
Lublin	5.5	51.2	327	−4.2	268.9	73.1
Prague	7.5	50.1	150	−2.8	270.3	67.8
Heidelberg	4.4	49.4	353	+1.4	274.5	91.0
Budapest	6.1	47.5	323	−1.3	271.8	84.3
Innsbruck	5.6	47.2	160	−6.2	266.9	80.4
Bucharest	3.1	44.4	146	−1.8	271.3	39.5

Table 5b. Correlation coefficients of parameters in Table 5a

	Attack rate	Animal fat	Latitude	Temperature	Hardness
Attack rate	–	+0.55[a]	+0.64[b]	−0.33	−0.57[a]
Animal fat	+0.55[a]	–	+0.50[c]	+0.21	−0.11
Latitude	+0.64[b]	+0.50[c]	–	−0.57[c]	−0.59[a]
Temperature	−0.33	+0.21	−0.57[c]	–	+0.44
Hardness	−0.57	−0.11	−0.59[a]	*+0.44*	–

[a] $P \leqslant 0.025$.
[b] $P \leqslant 0.01$.
[c] $P \leqslant 0.05$.

DISCUSSION

The present study revealed a significant negative association between the frequency of myocardial infarction in the communities studied and the hardness of the water supplies serving those communities, thus confirming a preliminary analysis carried out previously by one of the authors.[b] In that preliminary study, water hardness values were not weighted for population as in the present study and, therefore, some of the hardness values reported there differ from those shown in Table 2. However, there were no differences between the previous and the present analyses as to the tertile of the distribution into which each town fell. This association was in the direction found in other studies (soft water being associated with high infarction rates) (*5–7, 9, 10*) and of approximately the same order of magnitude as has been found in the United Kingdom (*6, 7*). Of course, it is well understood that water hardness is to be considered only as an indicator of some other factor, either in the water (e.g., the presence of beneficial minerals or the absence of harmful ones) or in the environment, which in turn is associated with water hardness. However, since hardness is a convenient factor to use and it is routinely determined, most studies use this indicator.

Taken in isolation, the body of data provided by the present investigation is not quite convincing of a causal relationship, since increasing incidence of myocardial infarction is also associated with more northerly latitudes. In other words, the more northerly countries have both a higher rate of cardiovascular mortality and softer water. However, latitude in itself cannot be causal and must be reflecting other environmental (e.g., temperature), behavioural (e.g., diet), or genetic factors that may be causal. These points are discussed below.

Climate

The climatic hypothesis has never been very clearly specified. Its proponents point to seasonal variations in mortality from IHD as demonstrating that climate affects disease frequency, and assume that climate is an obvious explanation of geographic differences. In the United Kingdom, however, the maximum seasonal fluctuation in mortality from IHD is smaller than the area differences observed and yet the variation in climate across the United Kingdom is very modest (*6*). Data reported previously (*4*) and in the present paper fail to show that temperature and other weather variables are connected in a clear-cut way with the occurrence of myocardial infarction. Elwood et al. (*11*) also found practically no association between IHD and temperature, although they did find an association with water hardness.

As the present data show, climate is not necessarily more extreme at more northerly latitudes. For instance Bucharest, the southernmost city of the register network, has a much lower myocardial infarction rate, but also a lower minimum average yearly temperature, than Dublin. Innsbruck is no warmer than Helsinki (Table 5), yet its myocardial infarction rate is much lower. Indeed, only a weak and nonsignificant association was found between lowest mean yearly temperature and the occurrence of IHD.

The relationship between water hardness and latitude arises from the geological trends across the continent. The geographical distribution of cardiovascular diseases in Europe as a function of

[b] MASIRONI, R. Report of the first meeting of the WHO Reference Centre Advisory Committee on Studies of Cardiovascular Diseases in Relation to Water Quality, Ottawa, 14-15 May 1976. WHO unpublished document.

latitude, geochemical environment, and water hardness has been studied by Masironi (*12, 13*). Northern countries with a higher cardiovascular death rate are underlain by very old geological substrata; these are poor sources of minerals essential to life and the waters there are, as a consequence, soft. In Europe, this pattern occurs in a north–south direction, but a similar association of higher cardiovascular mortality with lower levels of trace elements in soils and water is present in the United States in an east–west direction (*9, 14, 20*). Latitude, therefore, does not seem to play the same role in cardiovascular mortality in western Europe and North America, whereas water hardness always shows the same type of relationship with cardiovascular mortality in both continents.

Dietary factors

The positive correlation (+0.55) found between national daily fat consumption per person and IHD rates might suggest that higher attack rates in northern areas are really due to higher fat consumption rather than to water softness. Dietary differences must therefore be considered as a possible alternative. There is a relatively clear biological mechanism involved in the relationship between fat consumption and IHD, whereas this is one of the great weaknesses of the water hardness hypothesis. However, diet cannot be the explanation within the United Kingdom, where mortality rates across the country may differ by as much as 2 to 1 and the communities with high mortality rates have diets with a *lower* percentage of calories obtained from fats (*15*). Similarly, it is unlikely that marked dietary differences exist within the United States or Canada to explain the marked geographical differences in cardiovascular mortality rates that occur across those countries in association with water hardness. In other words, while the dietary fat hypothesis may hold true on an international basis to explain in part national differences in cardiovascular mortality rates, it does not seem to apply within countries, whereas the water hardness hypothesis is valid both internationally and intranationally in different studies.

Genetic factors

Mitchell (*16*) found an association between higher IHD mortality and the frequency of occurrence of blood group O in the United Kingdom and also internationally, which seems to be similar to the association between IHD mortality and water hardness. This is an avenue of research worthy of consideration.

Clayton (*15*), considering various explanations for the very considerable variation in mortality rates from cardiovascular diseases in the United Kingdom, e.g., water hardness (*7*), climate (*17*), diet, including dietary calcium (*18*) and hardened fats (*19*), and socioeconomic (*7*) and genetic factors (*16*), concluded that all these are basically alternative explanations of a smooth northwest-to-southeast gradient of mortality rates in that country, and that anything that varies along this axis will be automatically related to mortality. The data do not discriminate between rival hypotheses and investigators have retreated into multiple regression analysis and vigorous argument as to the interpretation of the resultant coefficients. However, it is unlikely that the same interrelationships that tend to confound the link between water hardness and cardiovascular disease in the United Kingdom exist to a comparable degree in other countries where soft-water areas have higher mortality than hard-water areas.

The question is really a broader one–has the disease the same pathology in areas where it is common as in areas where it is rarer? In other words, is it simply *more of the same* disease process or a different process? This is the traditional difficulty for the water hardness hypothesis in the way it has been investigated so far: water hardness is a geographical variable and varies according to broad geographical patterns. Unfortunately, other factors also vary in a similar manner.

Since it is practically impossible to investigate the influence of water hardness by a controlled experiment with sufficient replication of communities, progress may only be achieved by "experiments of nature". Two types of such experiment are relevant: (*a*) cross-sectional studies of area variation in water hardness versus geographical pathology; and (*b*) prospective studies of communities experiencing *changes* in water hardness. It is highly unlikely that prospective studies could be arranged on a sufficiently large scale and in sufficient numbers to test the causal hypothesis. Therefore, the former type of study, which has been carried out by several investigators in the past and of which the present investigation is an example, has considerable utility, although it cannot provide any direct answer as to whether the association is a causal one. Large retrospective studies can, however, be of use if a

large enough number of them consistently show an inverse association between water hardness and cardiovascular mortality, as this could be indirect proof that it is not merely a casual statistical association and may possibly contribute to the geographical variation in cardiovascular diseases.

ACKNOWLEDGEMENTS

This investigation was made possible with the help of the following investigators who provided us with water hardness data; they are thanked most sincerely:

Dr I. Gyarfas, Hungarian Institute of Cardiology, Budapest; Dr A. Radic, Medico-Social Research Board, Dublin, Ireland; Dr H. Tunstall Pedoe, St Mary's Hospital Medical School, London, England; Dr E. Lindo, Central Hospital, Tampere, Finland; Dr C. D. Furberg, Department of Clinical Physiology, Boden, Sweden; Dr C. Adrian, ASCAR, Bucharest, Romania; Dr J. Traczyk, Laboratory for Water Control, Warsaw, Poland; Dr I. Wilhelmsen, Sahlgrenska Hospital, Gothenburg, Sweden; Professor M. Kedra, Cardiology Department, Medical Academy, Lublin, Poland; Dr B. V. Bekker, Verlengde Groenstraat 75, Nijmegen, Netherlands; Mr A. Graziadei, Stadtwerke Innsbrück, Innsbruck, Austria; Dr Z. Hejl, Institute of Clinical and Experimental Medicine, Prague, Czechoslovakia; Dr S. Böthig, Humbold University Medical School, Berlin, German Democratic Republic; Mr I. V. Rochlitz, Municipal Water Works, Heidelberg, Federal Republic of Germany; Professor E. Nüssel, Department for Clinical and Social Medicine, Heidelberg, Federal Republic of Germany; and Dr M. Romo, Finnish Heart Association, Helsinki, Finland.

Thanks are also due to Professor L. Neri, University of Ottawa, Canada, Dr E. I. Hamilton, Institute for Marine Environmental Research, Plymouth, England, and Professor A. G. Shaper, Royal Free Hospital School of Medicine, London, England for having read and commented on the manuscript.

RÉSUMÉ

INFARCTUS DU MYOCARDE ET DURETÉ DE L'EAU: ENQUÊTE DANS LE CADRE DU RÉSEAU OMS DE REGISTRES DE L'INFARCTUS DU MYOCARDE

Quinze centres établis dans de grandes villes européennes ont collaboré à une étude coordonnée par l'OMS sur l'incidence et la distribution géographique de l'infarctus du myocarde. Il s'agit des villes suivantes: Berlin, Boden, Bucarest, Budapest, Dublin, Göteborg, Heidelberg, Helsinki, Innsbruck, Londres, Lublin, Nimègue, Prague, Tampere et Varsovie. La distribution de l'infarctus du myocarde n'est pas uniforme et on constate généralement une incidence plus élevée dans les villes dont la situation est plus septentrionale. Les données recueillies sur la dureté de l'eau de boisson consommée par les populations étudiées ont été pondérées en fonction de la taille de chaque population. Une corrélation négative significative ($r = -0,5$) a été trouvée entre la dureté de l'eau et l'incidence standardisée selon l'âge et le sexe du premier accident cardiaque ainsi que des accidents ultérieurs. Les constatations faites corroborent les rapports de plusieurs autres auteurs qui avaient déjà signalé des associations négatives du même ordre dans divers pays. Dans la présente enquête, l'interprétation des résultats est rendue délicate par le fait que la plus forte incidence d'infarctus est constatée dans les villes du nord où coïncident une latitude plus élevée et une plus faible dureté de l'eau. La consommation de matières grasses est aussi plus élevée dans ces villes. Il faut cependant noter que l'analyse des données recueillies, comme celle d'autres rapports, ne permet pas de conclure que les taux plus élevés d'infarctus dans les villes septentrionales sont liés aux températures qui y règnent (la moyenne de celles-ci étant d'ailleurs parfois plus basse dans certaines villes au sud du réseau). On est inévitablement en présence, dans les enquêtes de cette nature, de tout un ensemble de facteurs pouvant jouer un rôle contribuant – tels que la latitude, la température, la pluviosité, le régime alimentaire et les conditions socio-économiques. On peut aussi considérer que la composition géologique des sols puisse influencer à son tour la dureté de l'eau. L'un des types d'étude possible porte sur la variation respective de la dureté de l'eau et de la pathologie cardio-vasculaire selon la région. C'est à ce type d'étude transversale que se rattache la présente enquête, les études longitudinales (évolution dans le temps de la dureté de l'eau) étant plus difficiles à réaliser à grande échelle. En dépit du nombre des facteurs contribuants qui sont présents et qui varient dans les diverses enquêtes transversales, on constate que la dureté de l'eau est celui qui joue le rôle le plus constant dans toutes les études, et l'importance de ce facteur, c'est-à-dire de la composition chimique de l'eau, ne saurait être sous-estimée dans l'étiologie des maladies cardio-vasculaires.

REFERENCES

1. KOBAYASHI, J. *Bericht des Ohara Instituts für landwirtschaftliche Biologie,* **11**: 12 (1957).
2. AMAVIS, R. ET AL., ED. *Proceedings of the European Scientific Colloquium on Hardness of Drinking Water and Public Health, Luxembourg, May 1975.* Oxford, Pergamon Press, 1976.
3. NERI, L. & JOHANSEN, H. *Annals of the New York Academy of Sciences* **304**: 203 (1978).
4. *Myocardial Infarction Community Registers.* Copenhagen, WHO Regional Office for Europe, 1976 (Public Health in Europe, No. 5).
5. ANDERSON, T. W. & LE RICHE, W. H. *Canadian Medical Association journal,* **105**: 155 (1971).
6. CRAWFORD, M. D. ET AL. *Lancet,* **1**: 827 (1968).
7. CRAWFORD, M. D. ET AL. *Journal of chronic diseases,* **30**: 69 (1977).
8. KEYS, A., ED. *Circulation,* **41**: Suppl. I (1970).
9. SCHROEDER, H. A. *Journal of the American Medical Association,* **195**: 81 (1966).
10. NERI, L. C. ET AL. *Lancet,* **1**: 931 (1972).
11. ELWOOD, P. C. ET AL. *British journal of preventive and social medicine,* **31**: 178 (1977).
12. MASIRONI, R. ET AL. *Bulletin of the World Health Organization,* **47**: 139 (1972).
13. MASIRONI, R. *Geochemistry and the environment,* Vol. 2. Report of a Workshop, Capon Springs, West Virginia, May 1973. Washington, DC, National Academy of Sciences, 1977.
14. SAUER, H. I. *American journal of public health,* **52**: 94 (1962).
15. CLAYTON, D. G. In: Amavis, R. et ad., ed. *Proceedings of the European Scientific Colloquium on Hardness of Drinking Water and Public Health, Luxembourg, May 1975.* Oxford, Pergamon Press, 1976, p. 323.
16. MITCHELL, J. R. A. *Lancet,* **1**: 295 (1977).
17. ROBERTS, C. J. & LLOYD, S. *Lancet,* **1**: 1091 (1972).
18. KNOX, E. G. *Lancet,* **1**: 1465 (1973).
19. THOMAS, A. *British journal of preventive and social medicine,* **29**: 82 (1975).
20. SHACKLETTE, H. T. ET AL. *Elemental composition of surficial materials in the conterminous United States.* Washington, DC, US Printing Office, 1971 (Geological Survey Profile Paper 574-D).