Geochemistry of ground water and the incidence of acute myocardial infarction in Finland

A Kousa, E Moltchanova, M Viik-Kajander, M Rytkönen, J Tuomilehto, T Tarvainen, M Karvonen, for the Spat Study Group

Study objective: To examine the association of spatial variation in acute myocardial infarction (AMI) incidence and its putative environmental determinants in ground water such as total water hardness, the concentration of calcium, magnesium, fluoride, iron, copper, zinc, nitrate, and aluminium.

Design: Small area study using Bayesian modelling and the geo-referenced data aggregated into 10 km x 10 km cells.

Setting: The population data were obtained from Statistics Finland, AMI case data from the National Death Register and the Hospital Discharge Register, and the geochemical data from hydrogeochemical database of Geological Survey of Finland.

Participants: A total of 18 946 men aged 35–74 years with the first AMI attack in the years 1983, 1988, and 1993.

Main results: One unit (in German degree dH) increment in water hardness decreased the risk of AMI by 1%. Geochemical elements in ground water included in this study did not show a statistically significant effect on the incidence and spatial variation of AMI, even though suggestive findings were detected for fluoride (protective), iron and copper (increasing).

Conclusions: The results of this study with more specific Bayesian statistical analysis confirm findings from earlier observations of the inverse relation between water hardness and coronary heart disease. The role of environmental geochemistry in the geographical variation of the AMI incidence should be studied further in more detail incorporating the individual intake of both food borne and water borne nutrients. Geochemical-spatial analysis provides a basis for the selection of areas suitable for such research.

Abbreviations: CVD, cardiovascular disease; AMI, acute myocardial infarction; CHD, coronary heart disease
weight. The value of the cell is a weighted median of sample values.25–26

Bayesian spatial conditional autoregressive model (CAR) with covariates, which is currently in wide use in the field of the disease mapping, was applied in this study.27–30 Because Finland is sparsely inhabited, we propose one modification, which is pertinent to the sparsely populated areas. In the case of the 10 km x 10 km grid over Finland (excluding Lapland), some grid cells are empty and have to be omitted from the analysis; thus 5% of cells would be omitted. However, once we take environmental factors into account, assuming that the disease risk is influenced by both demographic factors (that is, people who actually live within the grid cell) and environmental factors in each cell whether or not it is inhabited, the omission of unpopulated cells results in a loss of information. The covariates included in the model were the age of onset of AMI and the levels of geochemical compounds in the ground water. The following modification is thus proposed.

Let \( Y_{ik} \) denote the number of cases in the cell \( i \) and age group \( k \). Furthermore, let \( N_{ik} \) denote the respective population at risk. The proposed probability distribution is then as follows:

\[
P(Y_{ik} = y | N_{ik}, \mu_{ik}) = \begin{cases} 
\frac{e^{-N_{ik} \mu_{ik}} (N_{ik} \mu_{ik})^y}{y!} & \text{if } 0 \leq y \leq N_{ik} \\
0 & \text{elsewhere}
\end{cases}
\]

that is, the Poisson distribution is assigned to the inhabited cells and the uninhabited cells naturally have no cases of the disease with the unit probability. Also we assign common regression structure to the \( \mu_{ik} \):

\[
\log(\mu_{ik}) = \alpha + \lambda_i + \beta_k + \xi Z_i + \log(N_{ik}) \quad \text{if } N_{ik} > 0
\]

\[
\log(\mu_{ik}) = \alpha + \lambda_i + \beta_k + \xi Z_i \quad \text{if } N_{ik} = 0
\]

where

- \( \alpha \) is the baseline risk
- \( \lambda_i \) is the local unexplained spatial random effect
- \( \beta_k \) is the effect of age group \( k \) on the risk level
- \( K \) is the age group, \( k = 0, \ldots, K \)
- \( \xi \) is a vector of environmental covariate effects
- \( Z_i \) is a vector of environmental covariates for area \( i \).

In this analysis, the age axis was divided into eight, five age groups: 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and 70–74. A non-proportional hazard model described their effect, which for AMI is more appropriate than the proportional hazards.

As outlined in the preceding section seven geochemical covariates were included in the analysis.

The regression coefficients \( \beta \) and \( \xi \) were given non-informative Normal priors \( N(0,0.00001) \), the background level \( \alpha \) was given an improper flat prior

\[
p(\alpha) \propto 1
\]

and the \( \lambda \) were given a CAR structure:

\[
\lambda_i \sim N(\lambda_{-i}, \tau m_i)
\]

where

- \( \lambda_{-i} \) are spatial variation parameters in the neighbourhood of \( i \)
- \( m_i \) is the number of neighbors for cell \( i \)
- \( \tau \) is the overall level of spatial precision (inverse spatial variation)

In the CAR models a neighbourhood structure needs to be defined. The neighbours were defined to be all those cells adjacent to the cell \( i \) through side or corner. Thus each cell could have at most eight (8) neighbours.

The model was fitted using WinBUGS. A total of 10 000 iterations with 5000 burn-in were run. “Burn-in” denotes iterations, which were discarded because of non-convergence of the model at the early stages of the algorithm. The evaluation of the test results showed that a satisfactory convergence was reached.

The posterior joint and marginal distributions of the parameters of interest were estimated and summarised. The 95% highest density regions (HDR), defined as most compact set of parameter values the posterior density mass over which is p/100, is used in Bayesian statistics to describe the variability of the estimate. It is thus by its nature somewhat similar to the frequentist confidence interval.

RESULTS

Age group and the total water hardness, Ca, Mg, Fe, F, Cu, Al, Zn, and NO₃⁻ concentrations in the ground water were included in the analyses as covariates. The overall age adjusted incidence of AMI among men aged 35–74 year was 480/100 000/year (posterior 95% HDR 473, 487). Table 1 gives information on the chemical contents of ground water. Table 2 illustrates the number of AMI cases, population at risk, and AMI incidence by age and water hardness. One unit (°dH) increment in water hardness decreased the risk of AMI by 1% (table 3). The levels of other geochemical elements included in this study did not have any additional effect on the spatial variation of the incidence of AMI.

DISCUSSION

The large geographical variation and changes in the incidence of AMI in Finland cannot be explained by individual lifestyle or genetic factors alone; environmental exposures must also contribute to the development of the disease. The classic risk factors and socioeconomic status provide only a partial explanation for the excess CHD risk in eastern Finland.31 The age distribution of the population did not have an effect on the geographical variation of the incidence of AMI. The results support the early observations of the inverse relation between the AMI incidence and total water hardness. An

<table>
<thead>
<tr>
<th>Element</th>
<th>Median</th>
<th>Mean</th>
<th>SD</th>
<th>25%</th>
<th>75%</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water hardness (°dH)</td>
<td>2.8</td>
<td>3.8</td>
<td>10.0</td>
<td>1.3</td>
<td>4.9</td>
<td>3621</td>
</tr>
<tr>
<td>Ca (mg/l)</td>
<td>14.4</td>
<td>19.9</td>
<td>67.3</td>
<td>6.9</td>
<td>24.4</td>
<td>3621</td>
</tr>
<tr>
<td>Mg (mg/l)</td>
<td>3.3</td>
<td>4.8</td>
<td>5.6</td>
<td>5.3</td>
<td>6.5</td>
<td>3621</td>
</tr>
<tr>
<td>Zn (mg/l)</td>
<td>11.4</td>
<td>51.4</td>
<td>231.8</td>
<td>3.9</td>
<td>36.8</td>
<td>3621</td>
</tr>
<tr>
<td>Al (mg/l)</td>
<td>10.4</td>
<td>88.1</td>
<td>310.7</td>
<td>1.7</td>
<td>61.4</td>
<td>3621</td>
</tr>
<tr>
<td>Cu (mg/l)</td>
<td>2.4</td>
<td>14.5</td>
<td>41.9</td>
<td>0.6</td>
<td>9.8</td>
<td>3621</td>
</tr>
<tr>
<td>F (mg/l)</td>
<td>0.1</td>
<td>0.4</td>
<td>0.6</td>
<td>0.1</td>
<td>0.3</td>
<td>12407</td>
</tr>
<tr>
<td>Fe (mg/l)</td>
<td>0.0</td>
<td>0.3</td>
<td>1.4</td>
<td>0.0</td>
<td>0.1</td>
<td>3621</td>
</tr>
<tr>
<td>NO₃⁻ (mg/l)</td>
<td>1.0</td>
<td>5.8</td>
<td>12.1</td>
<td>0.2</td>
<td>5.9</td>
<td>4039</td>
</tr>
</tbody>
</table>
The individual level. and the difficulty to apply results from ecological studies at may be related to the complexity of the ecological analysis.

Some previous studies have shown that a large number of water-borne nutrients should incorporate environmental exposure or control for it.

Table 2 Number of AMI cases, population at risk, and the AMI incidence per year by age and water hardness among 35 to 74 year old men in Finland in 1983, 1988, and 1993 (pooled data)

<table>
<thead>
<tr>
<th>Water hardness (°dH)</th>
<th>Age</th>
<th>AMI cases</th>
<th>Population at risk</th>
<th>AMI incidence</th>
<th>AMI cases</th>
<th>Population at risk</th>
<th>AMI incidence</th>
<th>AMI cases</th>
<th>Population at risk</th>
<th>AMI incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35–39</td>
<td>49</td>
<td>68730</td>
<td>71.3</td>
<td>282</td>
<td>506395</td>
<td>55.7</td>
<td>30615</td>
<td>51.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40–44</td>
<td>124</td>
<td>63250</td>
<td>70.8</td>
<td>675</td>
<td>468014</td>
<td>54.2</td>
<td>1840</td>
<td>51.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45–49</td>
<td>180</td>
<td>55485</td>
<td>72.4</td>
<td>1144</td>
<td>409953</td>
<td>279.1</td>
<td>47</td>
<td>325.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50–54</td>
<td>332</td>
<td>50500</td>
<td>65.7</td>
<td>1162</td>
<td>350975</td>
<td>473.5</td>
<td>63</td>
<td>506.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55–59</td>
<td>447</td>
<td>51842</td>
<td>86.2</td>
<td>2446</td>
<td>341606</td>
<td>716</td>
<td>71</td>
<td>582.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60–64</td>
<td>487</td>
<td>52081</td>
<td>83.1</td>
<td>2820</td>
<td>333483</td>
<td>845.6</td>
<td>97</td>
<td>860.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65–69</td>
<td>533</td>
<td>47996</td>
<td>1110.5</td>
<td>3139</td>
<td>306651</td>
<td>1023.6</td>
<td>101</td>
<td>1094</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70–74</td>
<td>606</td>
<td>42334</td>
<td>1431.5</td>
<td>3181</td>
<td>271337</td>
<td>1172.3</td>
<td>105</td>
<td>1010.2</td>
<td></td>
</tr>
<tr>
<td>Age standardised</td>
<td></td>
<td>2758</td>
<td>431488</td>
<td>562.1</td>
<td>15349</td>
<td>2988414</td>
<td>469.5</td>
<td>513</td>
<td>437.6</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Estimated effects of the geochemical covariates on the incidence of the first AMI among 35–74 year old Finnish men in 1983, 1988, and 1993 (pooled data)

<table>
<thead>
<tr>
<th>Element</th>
<th>Posterior mean</th>
<th>95% HDR (high density region)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total water hardness (°dH)*</td>
<td>−0.0097</td>
<td>(−0.0214 to −0.0003)</td>
</tr>
<tr>
<td>Zn (μg/l)</td>
<td>−0.0007</td>
<td>(−0.0061 to 0.0048)</td>
</tr>
<tr>
<td>Al (μg/l)</td>
<td>−0.0003</td>
<td>(−0.0007 to 0.0002)</td>
</tr>
<tr>
<td>Cu (μg/l)</td>
<td>0.0401</td>
<td>(0.0053 to 0.1477)</td>
</tr>
<tr>
<td>F (mg/l)</td>
<td>−0.0317</td>
<td>(−0.1453 to 0.0899)</td>
</tr>
<tr>
<td>Fe (mg/l)</td>
<td>0.0105</td>
<td>(−0.1298 to 0.3176)</td>
</tr>
<tr>
<td>NO3 (mg/l)</td>
<td>0.0066</td>
<td>(−0.0004 to 0.0016)</td>
</tr>
</tbody>
</table>

*Statistically significant effect. For example, one unit increment of Cu on average increases the AMI risk by 4% (posterior mean = 0.0401).

Inverse relation between water hardness and CVD mortality has been detected in several studies. They have suggested that CHD mortality can be related to the amount of magnesium and calcium in drinking water. In this study one mg/l increment in the fluoride concentration in the drinking water was associated with a 3% decrease in the risk of AMI.

CHD has a multifactorial aetiology. The method of spatial analysis used in this study is especially useful for testing the impact of several factors simultaneously. The validity of the Bayesian method used in this study has been also demonstrated earlier studies. Additional simulations have been run to check the validity of the proposed changes to it regarding the inclusion of the uninhabited cells in the analysis.

Ground water reflects the contents of trace elements in soil and bedrock but only a small proportion of the population use locally produced food supplies, cereals, and vegetables. Individual studies on the role of intake of both food and water-borne nutrients should incorporate environmental exposure or control for it.

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