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ORIGINAL ARTICLE

Homocysteine concentration and the risk of death in the adult Polish population

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Abstract

Background: Although there is a considerable epidemiologic evidence for a relation between homocysteine (Hcy) level and cardiovascular disease (CVD). The role of Hcy as a causal risk factor remains controversial.

Aim: To determine associations between Hcy level and all-cause and cardiovascular mortality in general population of Poland.

Methods: Within the frame of the National Multicenter Health Survey (WOBASZ), a representative sample of whole Polish population aged 20–74 was screened in years 2003–2005 and prospectively followed up until 2009. Baseline determinations, among other classical risk factors, included Hcy level in 7165 responders, performed by an immunoenzymatic method using IMMULITE 1 analyser and DPC reagents. Survival rates were followed up until 2009 and average follow up time was 5.4 years.

Results: During the 38,818.9 person-years of follow-up there were 270 deaths including 108 due to CVD, 37 due to coronary heart disease and 21 due to stroke. The relative risk of all-cause and CVD mortality was significantly higher in the highest (> 10.51 μmol/L) compared to the lowest (< 8.20 μmol/L) Hcy tercile in crude and multivariable proportional hazards models adjusted for sex, age, smoking status, hypertension, body mass index, total cholesterol, glucose and high sensitivity-C-reactive protein. Hazards ratios (95% confidence intervals) were as follows: all-cause mortality HR (95% CI): crude = 4.528 (2.947–6.154), multivariable-adjusted = 1.766 (1.197–2.605), CVD mortality crude = 4.322 (2.426–7.700), multivariable-adjusted = 1.937 (1.051–3.569).

Conclusions: In Polish adult population Hcy concentration is independently associated with all-cause and CVD mortality.

Key words: homocysteine, mortality, risk of death, cardiovascular disease, follow-up study, Polish population

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INTRODUCTION

Cardiovascular disease (CVD) and cardiovascular mortality continue to be a significant health and social problem in Poland. The association of CVD with the commonly recognised traditional risk factors, such as hypertension, dyslipidaemia, diabetes mellitus, smoking and obesity no longer raises any doubt. However, the significance of homocysteine (Hcy) in the pathogenesis of CVD is unclear, although the mechanisms underlying the atherogenic effects of elevated levels of this amino acid have been elucidated [1]. The evidence to support the association of Hcy concentration with CVD mainly originates from cross-sectional and case control studies. As regards prospective studies, there are certain controversies: most of these studies have shown a strong relationship between these factors [2–5], some of them have shown a weaker association [2], while the remaining ones have demonstrated no association [6, 7].

Given the considerable prevalence of hyperhomocysteinaemia in Poland (26% of males and 16% of females have elevated Hcy levels above 12 μmol/L [8]) we decided to analyse this topic, adopting mortality rate as a measure of the health of the society.

The aim of the study was to determine the association of Hcy concentration with all-cause mortality and cardiovascular mortality in a representative sample of adult inhabitants of Poland.

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METHODS

Study population

The material for analysis consisted in the data obtained from the Polish National Multicentre Health Survey (WOBASZ, *Wieloośrodkowe Ogólnopolskie Badanie Stanu Zdrowia Ludności*). The study was conducted between 2003 and 2005 and included a representative random sample of the inhabitants of Poland aged 20 to 74 years (6392 males and 7153 females). The aims, scope and methods of the WOBASZ study, selection of the study sample and the effect of nutritional factors on Hcy concentration are presented elsewhere [9, 10]. Below is a brief summary of information relevant for this paper only.

In all respondents, based on the questionnaires, physical examinations and laboratory tests a wide range of traditional cardiovascular risk factors were assessed. Serum Hcy levels were determined in 50% of sampled subjects. Venous blood sampling was carried out following at least 12 h of fasting, with the use of a uniform vacuum blood sampling system. The sampled blood was left at room temperature for approximately 30–60 min and was then centrifuged. The centrifuged serum (showing no signs of haemolysis) was frozen at –20°C and then transported in containers with dry ice to the Institute of Cardiology, Warsaw, Poland.

Determinations of Hcy levels and the other biochemistry parameters were carried out at a single central laboratory (Diagnostyka Sp. z o.o.), which participates in standardisation programmes conducted by the CDC (Atlanta, USA) and in the European programme RANDOX and has its field laboratory at the Institute of Cardiology, Warsaw, Poland. Serum Hcy levels were determined with the use of a solid-phase competition ELISA in which chemiluminescence was used to monitor the index enzymatic reaction. Alkaline phosphatase linked to *S*-adenosyl-L-homocysteine was used as the enzyme. Hcy levels were determined using the IMMULITE 1 system and reagents from DPC.

We analysed a total of 7165 fully evaluable respondents.

Mortality

The participants of the WOBASZ study were followed up for survival until the end of 2009 and involved an annual registration of deaths and their causes. Information on deaths in the cohort was obtained from the State Statistical Office, which collects individual death cards. The causes of death were established according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems and the following classification was adopted:

- deaths in total — all-cause deaths,
- cardiovascular deaths (ICD-10 diagnosis codes I00-I99),
- deaths due to ischaemic heart disease (IHD) (ICD-10 diagnosis codes I20-I25),
- deaths due to cerebrovascular disease (ICD-10 diagnosis codes I60-I69).

Statistical methods

The results were analysed statistically using SAS version 9.2. The study population was divided into three groups according to the tercile distribution of Hcy concentrations. In order to determine the relative risks of all-cause mortality and of cardiovascular mortality in terms of Hcy concentration terciles we used the Cox proportional hazards model. Respective Hcy concentration terciles and adjusting variables were the independent variables and death was the described variable. Factors that could potentially affect mortality and that were determined in the WOBASZ study were adopted as adjusting variables. These included: sex, age, smoking status, hypertension, body mass index and the concentrations of total cholesterol, glucose and markers of inflammation (high sensitivity-C-reactive protein [hs-CRP]).

RESULTS

Our study has shown that there is a variability in the values of most of the traditional cardiovascular risk factors relative to Hcy concentrations. The higher terciles of Hcy concentration, the higher the percentage of persons with hypertension, persons with obesity, smokers and the lower the glucose levels were observed. In the third Hcy concentration tercile, compared to the first tercile, the percentage of patients with hypertension was higher by 86%, the percentage of patients with obesity was higher by 29% and the percentage of smokers was higher by 16% (Table 1).

Over a follow-up period of 38,818.9 patient-years, a total of 270 men and women among the 7165 respondents investigated in the WOBASZ study died, including 108 cardiovascular deaths. The most common causes of death among the patients who had died from cardiovascular causes were IHD (37 deaths) and stroke (21 deaths).

Due to the low number of deaths due to IHD and stroke in the individual Hcy concentration terciles the analyses were limited to all-cause mortality and cardiovascular mortality.

All-cause mortality

The all-cause mortality rate for the entire study population was 6.95 per 1000 person-years and it was five-fold higher in the third Hcy concentration tercile than it was in the first Hcy concentration tercile (Table 2). The risk of death in Model 1 (sex-adjusted) was significantly higher in the second and third terciles compared to the first tercile. However, after adjustment for the remaining factors that could potentially affect mortality, the adjusted risk of death was about 77% higher in patients with Hcy concentration exceeding 10.51 μmol/L (third tercile) relative to those in whom Hcy concentration was below 8.20 μmol/L (first tercile). The remaining factors that significantly affected the risk of mortality included: sex (women vs. men: RR = 0.406; 95% CI 0.308–0.537), age (RR for an age increment of 1 years = 1.082; 95% CI 1.069–1.096), smoking status (RR for smokers vs. non-smokers =

Table 1. Study population characteristics by homocysteine (Hcy) concentration terciles

Parameter	Hcy concentration terciles			P
	1st	2nd	3rd	
Hcy range [μmol/L]	< 8.20	8.20–10.50	> 10.50	
Mean Hcy concentration [μmol/L]	6.95	9.31	13.98	< 0.0001
Age [years]	40.2	45.0	51.9	< 0.0001
Percentage of persons with hypertension according to the WHO criteria	25.6	34.2	47.7	< 0.0001
Percentage of persons with body mass index ≥ 30 kg/m^2	18.7	21.1	24.2	< 0.0001
Percentage of smokers	31.4	35.5	36.4	0.0005
Glucose [mmol/L]	5.15	5.01	4.86	< 0.0001
Total cholesterol [mmol/L]	5.37	5.44	5.38	NS

Table 2. Relative risk (RR) for all-cause mortality in the entire study population and by homocysteine concentration terciles

	Homocysteine concentrations			
	All patients	1st tercile	2nd tercile	3rd tercile
Total number of deaths	270	35	61	174
Mortality rate (no. of deaths per 1000 person-years)*	6.95	2.67	4.66	13.81
Crude RR for mortality (95% CI)*		1	1.532 (1.009–2.326)	4.258 (2.947–6.154)
Adjusted RR for mortality (95% CI)**		1	1.028 (0.674–1.569)	1.766 (1.197–2.605)

*Adjusted for sex only; **adjusted for sex, age, smoking status, hypertension, body mass index and the concentrations of total cholesterol, glucose and high sensitivity-C-reactive protein; CI — confidence interval

Table 3. Relative risk (RR) for cardiovascular mortality in the entire study population and by homocysteine concentration terciles

	Homocysteine concentrations			
	All patients	1st tercile	2nd tercile	3rd tercile
Total number of deaths	108	14	18	76
Mortality rate (no. of deaths per 1000 person-years)*	2.78	1.07	1.37	6.03
Crude RR for mortality (95% CI)*		1	1.074 (0.533–2.166)	4.322 (2.426–7.700)
Adjusted RR for mortality (95% CI)**		1	0.747 (0.368–1.517)	1.937 (1.051–3.569)

*Adjusted for sex only; **adjusted for sex, age, smoking status, hypertension, body mass index and the concentrations of total cholesterol, glucose and high sensitivity-C-reactive protein; CI — confidence interval

= 1.535; 95% CI 1.171–2.012) and hs-CRP (RR for an increment of 1 mg/dL = 1.433; 95% CI 1.276–1.609).

Cardiovascular mortality

Cardiovascular mortality rate (mean: 2.78 per 1000 person-years), as in the case of all-cause mortality, reached the highest values in the third Hcy concentration tercile relative to the first tercile (6.03 vs. 1.07 per 1000 person-years) (Table 3). The risk of cardiovascular mortality, after adjustment for confounders, was 94% higher in the third tercile compared to the first tercile. In addition, the risk of death was affected by sex (RR for women vs. men = 0.295; 95% CI 0.184–0.473), age (RR for an increment of 1 year = 1.075; 95% CI 1.054–2.096) and hs-CRP (RR for an increment of 1 mg/dL = 1.458; 95% CI 1.199–1.773).

The chances of overall survival and of survival without cardiovascular mortality differed relative to the Hcy concentration tercile. The chances of survival fell with increasing Hcy levels (Figs. 1, 2).

DISCUSSION

Our results suggest an independent association of Hcy concentration with all-cause mortality and with cardiovascular mortality in adult inhabitants of Poland.

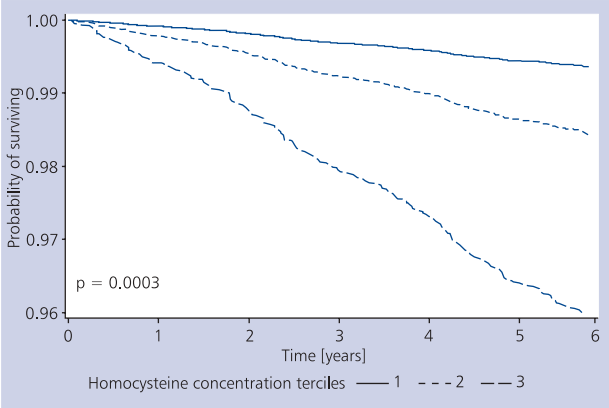

Figure 1. Probabilities of surviving 5.4 years in men by homocysteine concentration terciles

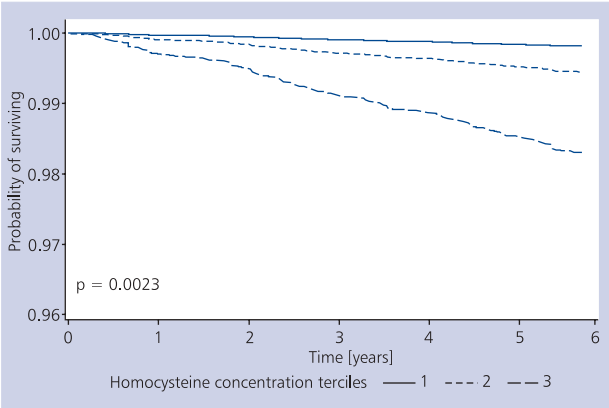

Figure 2. Probabilities of surviving 5.4 years without cardiovascular death in men by homocysteine concentration terciles

The highest risk of mortality from the analysed causes was observed in those patients whose Hcy concentration exceeded 10.51 μmol/L (RR for all-cause mortality = 1.766; 95% CI 1.197–2.605 and RR for cardiovascular mortality = 1.937; 95% CI 1.051–3.569) when the third tercile of Hcy concentration was compared with the first tercile. It should be added that the division of the respondents into Hcy concentration terciles was arbitrary and resulted from the relatively low number of deaths. Hence, the Hcy concentration cutoff value for the third tercile should not be treated as an absolute value above which the risk of death dramatically increases. The normal range for Hcy depends on many factors (sex, age, pregnancy, folic acid addition to foods) and is between 2.5th and 97.5th percentile of its distribution in the population. Generally, a large laboratory should have its own normal ranges for the population being assessed [11].

Of note is the fact that there have been no studies so far to assess the relationship between Hcy concentration and mortality in the Polish population. One advantage of the present study is the inclusion of additional adjusting factors in the model, which are rarely taken into account in other projects. Among these factors is, for instance, a marker of inflammation (hs-CRP).

Although the measurement of Hcy concentration in individuals participating in the WOBASZ study was performed on a one-off basis between 2003 and 2005, it most likely did not change during the follow-up. Hcy concentration is not a factor that dramatically fluctuates as a result of lifestyle, although it cannot be ruled out that in some individuals who had been taking folic acid supplements or vitamins B_6 or B_{12}, Hcy did change a little.

Our sample size was 7165 individuals, who were followed up for an average of 5.4 years. Given the low number of deaths due to IHD and stroke (e.g. only 1 person died in the first tercile of Hcy concentration), one limitation of the study was the impossibility to carry out analyses of mortality relative to the causes above mentioned. Such an assessment will only be possible in the later years of follow-up.

According to the currently conducted comparative analyses of the various assay methods for Hcy, the IMMULITE assay has shown the lowest precision of measurements [12], however between 2003 and 2005, the information on the limitations of this method were not known and some of the methods used at present time were not commonly available at the time of our study.

A certain limitation of the interpretation of our results is also the failure to take into account a full baseline health assessment of the study subjects. However, such an estimation exceeds the possibilities of a single cross-sectional epidemiological study.

The results of the WOBASZ study are consistent with most foreign projects investigating this issue, although when comparing the results of different studies one is advised to be cautious. Apart from the typical differences in the adopted methods of measurement, qualification criteria, follow-up duration and the set of adjusting variables, which were taken into account in the analyses, the results also depend on the health of the study population, the dynamics of health changes in time and on the levels of co-existing risk factors.

Results similar to those of the WOBASZ study have been obtained in the population of Ireland [13] and the elderly population of Spain [14] with respect to all-cause mortality, and in the populations of Japan [3], France [4], Finland [5], Norway [15], Israel [16], USA [17], UK [18] and the female population of Sweden [19] with respect to cardiovascular mortality.

In Ireland, where Hcy concentration was associated with all-cause mortality, the rates in the highest vs. lowest quartile of Hcy concentration were 2.1 (95% Cl 1.02–5.17) times higher [13]. In the elderly population of Spain, on the other hand, who were free from manifestations of civilisation-related diseases at the time of recruitment, a 2.3 times higher mortality rate was documented in individuals with Hcy levels exceeding 16.7 μmol/L compared to respondents with levels below 8.7 μmol/L [14].

In other studies: the Japanese JACC study [3] the French study [4] and the Finnish study [5], high Hcy concentrations were predictive of cardiovascular mortality — the risk of death in the highest vs. lowest quartile and terciles of Hcy concentration was 1.68 (95% CI 1.02–2.77) in the first, 1.29 (95% CI 1.01–1.65) in the second and 1.80 (95% CI 1.02–3.19) in the third study, after adjustment for confounding variables. In Finland, the high Hcy concentrations further increased cardiovascular mortality in men who smoked and had high levels of LDL-cholesterol, ApoB lipoprotein and fibrinogen [5]. In the Norwegian study [15], an increase in Hcy concentration of 5 μmol/L was associated with a 50% increase in cardiovascular morality.

In Jews over the age of 50 years a high level of Hcy was a marker of all-cause mortality with an RR of 1.97 (95% CI 1.31–2.98) and cardiovascular mortality with an RR of 1.81 (95% CI 1.19–2.76), when the fifth quintile was compared with the first one. This association seemed stronger in the first 5 years of follow-up [16]. In the elderly, both in the USA [17] and in the UK [18], Hcy concentration was associated with a higher cardiovascular mortality. In the highest vs. lowest tercile of Hcy concentration, the RR in the USA for mortality was 1.74 (95% CI 1.08–2.82) among individuals of American origin and 2.74 (95% CI 1.61–4.66) among individuals of Mexican origin, while RR in the UK was 1.96 (95% CI 1.39–2.78).

In Swedish females [19] followed up for 24 years, Hcy concentration proved an independent risk factor for both the occurrence of myocardial infarction and for mortality due to myocardial infarction.

Also the results of studies investigating individuals with pre-existing CVD have shown a relationship between Hcy concentration and the risk of death.

In a group of patients with angiographically confirmed IHD, Hcy concentration was a strong predictor of death in the US [20], irrespective of the traditional risk factors, CRP level and *MTHFR* gene polymorphism, and in Norway [21], where the risk of death was 4.5 times higher in the group of individuals with Hcy of $\geq$ 20 μmol/L, with respect to whom the level of this amino acid did not exceed 9.20 μmol/L.

In the elderly patients with IHD in the Framingham study [22] and in Chinese patients after stroke [23] the risk of death for the fourth vs. first Hcy concentration quartile, after adjustment for confounding variables, was 1.54 (95% CI 1.31––1.82) in the first and 1.75 (95% CI 1.3–2.4) in the second project for all-cause mortality and 1.52 (95% CI 1.16–1.98) for cardiovascular mortality in the first and 1.74 (95% CI 1.3––2.3) for stroke-related mortality in the second project.

In patients with myocardial infarction recruited at a cardiology ward in Greece, Hcy concentration did not significantly determine mortality [24].

While the association of Hcy concentration with all-cause mortality and cardiovascular mortality has been confirmed in observational epidemiological, prospective and retrospective studies, it seems essential to assess whether this is a causal relationship and whether reduction in Hcy concentration could contribute to a reduced risk of death. Demonstration of the causal relationship requires, however, randomised interventional studies. In three of them, NORVIT [25], HOPE [26, 27] and VISP [28], attempts to use high doses of vitamins B, which play an essential role in the metabolism of Hcy, despite the reduction in Hcy, failed to reduce mortality compared to placebo. The question still remains whether a high Hcy level is a causative factor for CVD or at least whether it is a marker of cardiovascular risk.

CONCLUSIONS

Our results show an independent association of Hcy concentration with all-cause mortality and cardiovascular mortality in adult inhabitants of Poland.

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Conflict of interest: *none declared*

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Stężenie homocysteiny a ryzyko zgonu ogółem i z powodu chorób sercowo-naczyniowych w populacji polskiej

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Streszczenie

Wstęp: Znaczenie homocysteiny (Hcy) w patogenezie chorób układu sercowo-naczyniowego (CVD) nie jest do końca jednoznaczne, mimo że wyjaśniono mechanizmy promiażdżycowego działania podwyższonych stężeń tego aminokwasu. Dowody na współzależność między stężeniem Hcy a CVD pochodzą głównie z badań przekrojowych i badań typu *case-control*, natomiast wśród badań prospektywnych istnieją pewne kontrowersje.

Cel: Celem pracy była ocena związku między stężeniem Hcy a umieralnością ogólną i spowodowaną CVD w populacji polskiej.

Metody: W latach 2003–2005 w ramach Wieloośrodkowego Ogólnopolskiego Badania Stanu Zdrowia Ludności (WOBASZ) zbadano reprezentatywną losową próbę mieszkańców Polski w wieku 20–74 lat. W badaniu początkowym, oprócz innych czynników ryzyka CVD, u 7165 respondentów oznaczono stężenie Hcy metodą immunoenzymatyczną, przy użyciu analizatora IMMULITE 1 i odczynników firmy DPC. Obserwację przeżycia tych osób prowadzono do końca 2009 r. i polegała na rejestracji przypadków zgonów i ich przyczyn na podstawie indywidualnych kart zgonów gromadzonych w GUS. Wyznaczono względne ryzyka zgonu ogółem i z powodu CVD w tercylach stężenia Hcy (1 tercyl < 8,20 μmol/l; 3 tercyl > 10,51 μmol/l) metodą proporcjonalnych hazardów Coxa. Zmiennymi adiustującymi były: płeć, wiek, palenie tytoniu, nadciśnienie tętnicze, wskaźnik masy ciała oraz stężenia cholesterolu, glukozy i hs-CRP.

Wyniki: W okresie obserwacji wynoszącej 38 818,9 osobolat wśród 7165 respondentów przebadanych w projekcie WOBASZ zmarło 270 mężczyzn i kobiet, w tym dla 108 osób przyczyną zgonu były CVD, dla 37 — choroba niedokrwienna serca, a dla 21 — udar mózgu. Współczynniki umieralności ogólnej wyniosły 13,81/1000 w trzecim i 2,67/1000 osobolat w pierwszym tercylu Hcy, a z powodu CVD odpowiednio 6,03/1000 i 1,07/1000 osobolat. Ryzyko zgonu ogółem i z powodu CVD, skorygowane o zmienne adiustujące, było istotnie wyższe w trzecim w porównaniu z pierwszym tercylem stężenia Hcy i przedstawiało się następująco — umieralność ogółem: RR (95% CI) surowe = 4,528 (2,947–6,154); adiustowane = 1,766 (1,197–2,605), umieralność z powodu CVD: surowe = 4,322 (2,426–7,700), adiustowane = 1,937 (1,051–3,569).

Wnioski: W dorosłej populacji polskiej zanotowano niezależny związek między stężeniem Hcy a ryzykiem zgonu ogółem i z powodu CVD.

Słowa kluczowe: homocysteina, umieralność, ryzyko zgonu, choroby układu sercowo-naczyniowe, badanie prospektywne, populacja polska

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