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Premature Parental Heart Attack is Heralding Elevated Risk in Their Offspring

Mirjana Rumboldt[1], Zvonko Rumboldt[2] and Serafina Pesenti[1]

[1] Department of Primary Care/Family Practice, School of Medicine, University of Split, Split, Croatia

[2] Department of Internal Medicine, University Hospital »Split«, Split, Croatia

A B S T R A C T

A small subgroup of children, whose parents have suffered a heart attack in their late thirties and early forties, may be at particularly high cardiovascular risk. University Hospital »Split« gives tertiary health care to some 700,000 people in southern Croatia and treats about 300 acute myocardial infarctions per year, with a 3–5% share in the age under 45 years. This cross-sectional, clinical and laboratory study included all the patients below the age limit of 45 years, treated for acute myocardial infarction between 1990 and 1995, complexively 55 of them, and their natural children, 97 all in all. The results were compared to those of a stratified children's sample taken from the population of the same region. The relative weight, blood pressure, and plasma cholesterol were significantly higher in these children than in the control group ($p < 0.05$). In 50 of these offspring (51.5%), in addition to the obviously positive family history, detected were further cardiovascular risk factors, defined as values above the 95th distribution percentile for age and gender. The average blood pressure, relative weight and cholesterol levels were even higher in these, »risky« children than in the studied sample ($p < 0.05$), and much more elevated than in the matching control pupils ($p < 0.001$). The most often detected risk factors were elevated cholesterol (in 44%), arterial hypertension (in 40%), obesity (in 32%), and smoking (in 24%). Most of the children (64%) had only one additional risk factor, while in the remaining 36% the most prevalent risk factors were overweight (in 14 out of 18) and arterial hypertension (in 11 out of 18). It is concluded that cardiovascular risk factor screening among children with a positive family history of premature atherosclerotic complications is appropriate and cost-effective.

***Key words**: cardiovascular diseases, epidemiology, risk factors, myocardial infarction, offspring*

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Introduction

There is some controversy about the indications for cardiovascular risk factor screening among children and youngsters. It is generally held that such an intervention is not recommended before adolescence because of low yield, high cost and too many false positive results[1–3]. It seems that a tiny subgroup (less than 1%) of such persons, whose parents have suffered a heart attack before their age of 45 could be at particularly high risk[4–8], and since easily identified, might be an exception to the rule. To evaluate this hypothesis we have performed the following cross -section study.

Patients and Methods

Clinical Hospital Split offers hospital services to a population of some 700,000 people in southern Croatia (Dalmatia) with an average of 300 acute myocardial infarctions (AMI) per year. In a five-year period (1991–1995) among 1,462 patients treated in this institution for AMI, identified were 55 consecutive subjects (3.8%) below the age of 45 (39.9 ± 4.2 years) with living children (48 fathers and 7 mothers). They and all their 97 living offspring (54 boys and 43 girls, aged 3–26 years; mean age 14.2 ± 4.8 years) were subsequently investigated by us for the standard cardiovascular risk factors[5]: the patients within the first 24 hours after admission and their children as soon as possible after the parent's discharge from the hospital (not more than 6 months later). All the measurements were performed with standard techniques[6]. The upper limits of »normal« values were defined at the 95th distribution percentile for age and sex[4–6], and did not surpass 124/84 mm Hg for blood pressure, 5.6 mmol/l for total cholesterol, 2.0 mmol/l for serum triglycerides, and 5.9 mmol/l for blood glucose[9].

The relative weight (RW) was expressed as a percent of measured body mass in kilograms and ideal weight for age and gender, according to the Metropolitan Life Insurance Company tables[10,11]. Overweight was defined as RW > 100 < 120, and obesity as RW ≥ 120. Body mass index (BMI) was calculated according to formula BMI = kg/m^2, i.e. body mass in kilograms divided by the squared body height in meters. Overweight was defined as BMI > 25 < 30, and obesity as BMI ≥ 30.

A subset of these children, having at least one risk factor identified in addition to the mandatory positive family history were analyzed separately as »risky« progeny.

The results were compared to those of a concurrently obtained, comparable but not exactly matching, stratified sample of the 4th grade school children from Split, in 1992–1993 (n = 139; 73 girls, 66 boys, aged 13–15 years; averaging 14.2 ± 0.6 years)[5]. The data were processed and tabulated; calculated were the means, standard deviations and 95 per cent confidence intervals (95% CI); the observed differences were assessed by chi-square test with Yates's correction (Fisher's test for small groups), or two-tailed, unpaired Student's t-test (the data distributions were acceptably »normal« since quite similar results were obtained using the non-parametric Mann-Whitney U test), and p value < 0.05 was considered statistically significant.

Results

The conventional cardiovascular risk factors were significantly higher in the coronary patients' descendants than in the control population, which was particularly true for the »risky« subset of these

TABLE 1
AVERAGE VALUES OF THE MOST IMPORTANT RISK FACTORS IN OFFSPRING OF AMI PARENTS (ALL, »AGE ADJUSTED«, AND »RISKY«) COMPARED TO CONTROL CHILDREN

	Control children (N = 139)	All AMI offspring (N = 97)	»Age adjusted« AMI offspring (7–19 yrs old) (N = 83)	»Risky« AMI offspring (N = 50)
Age (years)	14.2 ± 0.6	14.2 ± 4.8	14.1 ± 1.9	15.1 ± 4.7
Systolic BP (mm Hg)	114.3 ± 8.5	116.6 ± 15.3*	116.7 ± 10.4*	122.9 ± 17.0**
Diastolic BP (mm Hg)	73.6 ± 7.3	74.3 ± 12.7*	74.2 ± 10.1*	79.7 ± 13.3**
Cholesterol (mmol/l)	4.4 ± 0.6	5.2 ± 1.1*	5.2 ± 0.9*	5.4 ± 1.2**
Glucose (mmol/l)	5.1 ± 0.8	4.7 ± 0.7	4.6 ± 0.6	4.8 ± 0.5
Relative weight (%)	99.5 ± 11.2	103.8 ± 15.2*	102.9 ± 12.9*	110.1 ± 16.7**

*$p < 0.05$ vs. control; **$p < 0.001$ vs. control

children (Table 1). For example, the relative weight among 139 control children was lower than among 97 AMI descendants by 4.3% ($t = 2.50$; $p = 0.013$), and 10.6% less than in the »risky« subset ($t = 4.99$; $p < 0.0001$). The only exception to this trend was blood glucose (as expected in this age group). Unfortunately, the serum triglyceride levels could not be compared since these values have not been obtained in the control population.

Because of the wide age range among the AMI offspring (3–26 years) and possible influence of data heterogeneity, the third column in Table 1 presents the »age adjusted« subjects, i.e. only those 83 of 97 children that were beyond 7 and below 19 years of age at the time of examination (excluded were 3 persons under 7, and 11 above 19 years); the results are quite similar, however.

In this study, 50 out of 97 children, or 51.5% of the premature AMI descendants have had additional risk factors on top of an undoubtedly positive family history, and were labeled as »risky«. This clustering phenomenon was almost twice as high as in the control sample of the same age (51.5% vs. 25.9%; $\chi^2 = 17.3$, $p < 0.0001$). The most common risk factors were elevated cholesterol levels and arterial hypertension (27.8% and 20.6% in all, and 45% and 40% in the »risky« subgroup, respectively; p always < 0.001).

Table 2 presents the cardiovascular risk factors' prevalence in our subjects. Relatively few parents with only one risk factor (the »children« column totals more than 100% since all these examinees were obviously having positive family history by the inclusion criteria) are probably due to the questionably negative inheritance histories: not all the patients were interviewed directly by us, and some information were obtained from the available medical documentation which was

TABLE 2
RISK FACTORS PREVALENCE IN PARENTS WITH PREMATURE HEART ATTACK AND IN THEIR OFFSPRING*

	Parents (N = 55)	Offspring (N = 97)
1 risk factor	17 (30.9%)	97 (100%)
2 risk factors	22 (40.0%)	32 (33.0%)
3 risk factors	11 (20.0%)	11 (11.3%)
4 or more risk factors	5 (9.1%)	7 (7.2%)

* In this table the following risk factors were included: positive family history, arterial hypertension, smoking, obesity, hypercholesterolemia, hypertriglyceridemia, and hyperglycemia

not comprehensive enough all the time. Obviously, the parents were having more risk factors than their children; they were some 25 years (range 20–34 years) older as well. There were 38 smokers out of 55 parents (69.1% with 95% CI 55.2–80.9%), and 23 smokers out of 97 children (23.7% with 95% CI 15.7–33.4%; $\chi^2 = 28.2$, $p < 0.0001$).

Parental gender differences in the prevalence of risk factor were minor and mostly insignificant (Fischer exact test giving p value always above 0.85 except for triglycerides and overweight, which were more prevalent among mothers: 3/7 vs. 3/48, $p = 0.02$, and 2/7 vs. 1/48, $p = 0.04$, respectively).

Hypercholesterolemia was the most common risk factor among the analyzed children (27 out of 97 or 27.8 per cent; 95% CI 19.2–37.9%), followed by smoking (almost 24%), arterial hypertension (20/97 or 20.6 per cent; 95% CI 13.1–30.0%) and obesity (19/97 or 19.6 per cent; 95% CI 12.2–28.9%). Elevated levels of plasma triglycerides were found in only 2 (2.1%) children.

Table 3 shows the risk factor prevalence in the analyzed children, in the »risky« subset of them (having at least one risk factor on top of a positive family history), and in their parents. The occurrence of hypercholesterolemia and elevated blood pressure almost doubled in these 50 subjects compared to the entire sample of 97 (44.0% vs. 27.8%; $\chi^2 = 3.19$, $p = 0.07$, and 40.0% vs. 20.6%; $\chi^2 = 5.32$, $p = 0.02$, respectively). The high prevalence of obesity (19/97 or 19.6% in the entire sample, 18/55 or 32.7% among the »risky« children; $\chi^2 = 1.27$, $p = 0.26$) is in contrast to the lower figures in their parents (1/39 or 2.6% in the »risky« parents; $\chi^2 = 9.12$, $p = 0.003$; 8/55 or 14.5% in all the parents; $\chi^2 = 0.31$, $p = 0.58$), while the absence of concomitant hypertriglyceridemia is surprising. The smoking habit did not differ substantially from the entire sample (24.0 vs. 23.7% for children; 51.3% vs. 69.1% for parents; $\chi^2 = 2.36$, $p = 0.13$).

As shown on Table 4, the risk factor clustering was clearly more pronounced in parents than in their »risky« children (family history was omitted for the sake of comparability). For example, there were over 40% parents with two risk factors and only 22% such children ($\chi^2 = 4.97$; $p = 0.026$). Nevertheless, 36% of these descendants (95% CI 22.9–50.8%) were having at least two further risk factors in addition to positive family history. Among these 18 offspring, 14 were overweight (77.8%), 11 were hypertensive (61.1%), 10

TABLE 3
PREVALENCE (%) OF THE VARIOUS RISK FACTORS IN ALL AMI OFFSPRING'S SAMPLE, IN SUBSAMPLE OF »RISKY« OFFSPRING AND IN THEIR PARENTS*

	All AMI offspring (N = 97)	»Risky« offspring (N = 50)	Parents of »risky« offspring (N = 39)
Positive family history	100.0	100.0	74.4
Arterial hypertension	20.6	40.0	46.2
Hypercholesterolemia	27.8	44.0	51.3
Hypertriglyceridemia	2.1	0	12.8
Obesity	19.6	32.0	2.6
Smoking	23.7	24.0	51.3

* The »diabetes« or »glucose intolerance« row is not shown since there were no such patients in this study

TABLE 4
PREVALENCE OF ADDITIONAL RISK FACTORS IN »RISKY« OFFSPRING AND IN THEIR PARENTS*

	Offspring (N = 50)	Parents (N = 39)
1 risk factor	32 (64%)	11 (28.2%)
2 risk factors	11 (22%)	17 (43.6%)
3 risk factors	7 (14%)	8 (20.5%)
4 and more risk factors	0	3 (7.7%)

* The same risk factors as on Table 2 with the exception of family history

were hypercholesterolemic (55.6%), 7 were smokers (41.4%), and one was hypertriglyceridemic (5.5%).

It is noteworthy that there were no significant gender differences in the prevalence of any among the analyzed parameters (χ^2 always below 1.00; $p > 0.32$). The biggest but still insignificant discrepancy was registered in the smoking habit: there were 16/54 (29.6%) smokers among boys, and 7/43 (16.3%) among girls ($\chi^2 = 0.96$, $p = 0.32$).

Discussion

It is well known that cardiovascular risk factors can be identified already in childhood[6,12]. The »tracking« and »clustering« phenomena additionally underscore the importance of early detection for timely intervention, consisting mostly of dietary restrictions and other general measures[1,12]. Nevertheless, the debate about the appropriateness of childhood screening is still open because of its low yield and high cost/effectiveness ratio[2,3]. We[6,9] and others[2,12] have shown that more than 20% of school children have one or more statistically defined risk factors (values above the 90th percentile of distribution), but that in the subsequent years at least 30% of them regress toward the mean, entering the lower deciles of distribution. In the remaining, the risk factors, albeit variable, tend to maintain their rank order (tracking). If a perfect tracking were to exist, such children would be destined for adult disease, e.g. hypertension, hyperlipidemia or atherosclerosis. However, these trackings widely range from early to late childhood, e.g. their coefficients of correlation fluctuate from 0.1 to 0.7 for systolic, and from 0.02 to 0.5 for diastolic blood pressure in different studies[6]. We have previously shown that in the age between 11 and 18 years the estimated tracking ranges from the high correlation coefficients of 0.7–0.8 for cholesterol levels, 0.6–0.7 for relative weight and 0.5–0.6 for systolic blood pressure, to the low 0.3 for diastolic blood pressure or even less (below 0.1) for triglycerides[6].

A large portion of risk factors identified during childhood appears heritable, due to common genetic and environmental factors. The probability of adverse cardiovascular outcome increases not only with the individual level of aberration and mutual enhancement of risk factors, but also with a positive history of family aggregation. We have shown earlier[13] that the prevalence of cardiovascular risk factors was 3–5 times higher among parents of children at elevated risk than among the control parents (e.g. 57.1 vs. 11.8 per cent in boys; the highest clustering being observed for elevated serum cholesterol, resulting in linear correlation up to 0.558). In other words, elevated risk in children predicts a similar constellation in their parents. In the present study we have tested the inverse, hypothesizing that premature parental coronary heart disease is heralding elevated risk in their offspring. Such an approach was undertaken by others[4,5,7,8,14] as well, and similar results have been obtained. For instance, small discrepancies between the Ralidis et al. (1998)[8] and our results could, at least in part, be due to selection bias; e.g. our examinees were younger (par-

ents: below 45 vs. over 50 years, children: about 14 vs. over 16 years) than their Greek counterparts. Since our populations share a similar environment and mostly consume the same »Mediterranean« diet, some additional, concealed factors may be responsible for the rest of the difference.

Striking is the observed high prevalence of smoking among younger heart attack patients (almost 70%), the fact that was addressed previously[9]. Even more frustrating is the notion that nearly 25% of their teenage children are smokers too, urging for massive campaigning against cigarettes and for toughing antismoking legislation[15].

Obesity is another, theoretically easily remediable factor of adverse cardiovascular prognosis. Its high prevalence (nearing 20% in the whole sample, almost 25% among the »risky« children, similar to the US data[16]) calls for specific educational interventions within the population. The virtual absence of hypertriglyceridemia in this study is surprising since the two conditions are often associated[1,16]. It may be partly explained by meticulous preparation for blood sampling and clear instructions for overnight fasting.

Which are the limitations of this study? The first one is a relatively small number of examinees. It is almost impossible, however, except in large, multicentre trials, to include impressive numbers of young people with AMI (of course the definition of »young« or »premature AMI« is debatable, and some investigators have studied the offspring of such patients at or below 60 years of age at the time of heart attack[17]). Moreover, we did not measure important modifiable risk factors, such as HDL and LDL cholesterol, apolipoprotein B, Lp(a), coagulation abnormalities or homocysteine levels.

The title of this report is summing up our results: yes, a premature parental heart attack is heralding an elevated risk in their offspring. The operative message is clear: cardiovascular risk factors often aggregate (cluster), particularly in »stigmatized« children, so that a simple work-up in such persons is appropriate both in terms of yield and cost/benefit. The high prevalence of risk factors in the progeny of young people with coronary artery disease suggests that such children should be screened in this respect since

a) the number of persons with acute myocardial infarction below 45 years is low (less than 5% of the AMI population[9]), and their progeny is even more unusual among their peers (less than 1%);
b) although these children are exposed to significantly elevated risk, some risk factors are easily detected almost immediately (e.g. obesity, smoking), and others are inexpensively and reliably revealed in this highly selected group (e.g. hyperlipidemia, arterial hypertension)[1,4,5,8,12,14,16];
c) with simple measures, such as antismoking programs or dietary advices (in rare instances, specific interventions, such as statins in heterozygous familial hypercholesterolemia, are indicated), their risk may be drastically reduced.

A caveat against wide implementation of diagnostic and/or therapeutic measures adequate for tiny subgroups at very high risk to population at large is pertinent. The case is well illustrated by the implications of the famous statin studies[18], corroborated by the recent data from the LIFE, ARBITER (less so ALLHAT), and ASCOT trials[19]. We[18] have recently argued that »the relative absence of major adverse effects of statin therapy means that the degree of coronary risk at which therapeutic intervention is indicated can hardly be determined by the point at which benefit exceeds untoward effects. Huge numbers of apparently healthy individu-

als may therefore become candidates for such interventions... Ignoring the evident problems of efficacy and *compliance* (will the prescribed statins be adequately used by the majority or by just a tiny segment of the target population?), and *adverse effects* (although serious side -effects are rare, presumably ≤ 1‰ per year, their absolute number may become unacceptably high with large exposition and injudicious prescribing, as recently illustrated by many severe cases of rhabdomyolysis...), the main problem becomes *exceedingly high cost* of such a preventive intervention in the population, leaving to... decision makers the responsibility of adequate financial allocation of the available funds, which by definition are limited and hardly sufficient«. Indeed, the medical and financial costs of too wide and too aggressive, particularly drug -based, atherosclerosis prevention in childhood and adolescence can become frightening!

Conclusions

1. There is a high prevalence of cardiovascular risk factors in progeny of people suffering from heart attack in their late thirties and early forties.

2. These »stigmatized« children should therefore be screened for cardiovascular risk factors: the yield is high, the number to be assessed is low, and the cost of such an intervention is negligible.

3. Simple general measures, e.g. dietary interventions or antismoking programs, vigorously implemented to children at particularly elevated risk may have decisive prognostic impact.

REFERENCES

1. DANIELS, S. R., Curr. Atheroscler. Rep., 3 (2001) 479. — 2. KLAG, M. J., D. E. FORD, L. A. MEAD, N. Engl. J. Med., 328 (1993) 313. — 3. NEWMAN, T. B., W. S. BROWNER, S. B. HULLEY, J.A.M.A., 267 (1992) 100. — 4. LEE, J., R. M. LAVER, W. R. CLARKE, Pediatrics, 78 (1986) 330. — 5. COLDITZ, G. A., E. B. RIMM, E. GIOVANNUCCI, M. J. STAMPFER, B. ROSNER, W. C. WILLETT, Am. J. Cardiol., 67 (1991) 933. — 6. RUMBOLDT, M., Z. RUMBOLDT, S. PESENTI, Croat. Med. J., 34 (1993)143. — 7. JOUSILAHTI, P., P. PUSKA, E. VARTAINEN, J. PEKKANEN, J. TOUMILEHTO, J. Clin. Epidemiol., 49 (1996) 497. — 8. RALLIDIS, L. S., N. H. PAPAGEORGAKIS, A. A. MEGALOU, N. J. EXADACTYLOS, G. K. TSITOURIS, E. G. PAPASTERIADIS, Eur. Heart J., 19 (1998) 395. — 9. RUMBOLDT, Z., M. RUMBOLDT, Eur. Heart J., 19 (1998) 1410. — 10. HARRISON, G. G., Ann. Intern. Med., 103 (1985) 489. — 11. http://www.halls.md/ideal-weight/body.htm. — 12. BERENSON, G. S.: Causation of cardiovascular risk factors in children. (Raven Press, New York, 1986). — 13. RUMBOLDT, M., Z. RUMBOLDT, S. PESENTI, Liječ. Vjesn., 112 (1990) 361. — 14. HIPPE, M., J. VESTBO, A. M. BJERG, J. Epidemiol. Commun. Health, 51 (1997) 266. — 15. GILMORE, A. B., J. COLLIN, Br. Med. J., 325 (2002) 846. — 16. BAO, W., S. R. SRINIVASAN, R. VALDEZ, K. J. GREENLUND, W. A. WATTIGNEY, G. S. BERENSON, J.A.M.A., 278 (1997) 1749. — 17. CUOMO, S., P. GUARINI, G. GAETA, M. DE MICHELE, F. BOERI, J. DORN, M. G. BOND, M. TREVISAN, Eur. Heart J., 23 (2002) 1345. — 18. RUMBOLDT, Z., M. RUMBOLDT, Period. Biol., 104 (2002) 107. — 19. PASTERNAK, L. C, J.A.M.A., 288 (2002) 3042.

Z. Rumboldt

Department of Internal Medicine, University Hospital »Split«, Spinčićeva 1, 21000 Split, Croatia

SRČANI UDAR U OSOBA MLAĐIH OD 45 GODINA VJESNIK JE POVIŠENOG RIZIKA OBOLIJEVANJA NJIHOVE DJECE

S A Ž E T A K

Mala podskupina djece, čiji su roditelji doživjeli akutni koronarni incident u kasnim tridesetim ili ranim četrdesetim godinama, izložena je izrazito povišenom kardiovaskulnom riziku. Klinička bolnica Split pruža tercijarnu zdravstvenu zaštitu populaciji južne Hrvatske od nekih 700.000 ljudi i liječi oko 300 akutnih infarkta godišnje, od kojih 3–5% otpada na osobe ispod 45 godina. U ovom kliničkom i laboratorijskom istraživanju prevalencije obrađeni su svi bolesnici koji su u razdoblju između 1990. i 1995. godine imali manje od 45 godina, a liječeni su od akutnog infarkta miokarda, ukupno njih 55, kao i 97-oro njihove djece. Rezultati su uspoređeni s podacima stratificiranog uzorka školske djece slične dobi, iz iste regije. Utvrđeno je kako je ukupan uzorak djece koronaropata imao značajno veću relativnu težinu, arterijski tlak i kolesterolemiju nego kontrolna skupina ($p < 0,05$). Uz očito pozitivnu obiteljsku anamnezu, u 50 od ovih 97 potomaka (51,5%) otkriveni su i drugi čimbenici rizika, definirani vrijednostima iznad 95. percentila distribucije za dob i spol. Arterijski tlak, relativna težina i kolesterolemija bili su viši u ovoj, »rizičnoj« podskupini nego u cijelom uzorku potomaka koronaropata ($p < 0,05$) i mnogo viši nego u kontrolnoj skupini ($p < 0,001$). Najčešći čimbenici rizika bili su hiperkolesterolemija (u 44%), hipertenzija (u 40%), pretilost (u 32%) i pušenje (u 24%). Većina djece (64%) imala je samo jedan dodatni čimbenik rizika, dok su u preostalih 36% najčešći bili preuhranjenost (14/18) i arterijska hipertenzija (11/18). Zaključuje se da je probir na kardiovaskulne čimbenike rizika u djece s pozitivnom obiteljskom anamnezom ranih aterosklerotskih komplikacija isplativ i svrsishodan.