EJPC-D-21-01052 Revised Form

Maternal hypercholesterolemia during pregnancy affects severity of myocardial infarction in young adults

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ABSTRACT

Aims Elevated maternal cholesterol during pregnancy (MCP) enhances atherogenesis in childhood, but its possible impact on acute myocardial infarction (AMI) in adults is unknown.

Methods and results We retrospectively evaluated 310 patients who were admitted to hospital and whose MCP data were retrievable. 89 AMI patients with typical chest pain, transmural infarction Q-waves, elevated creatinine kinase and 221 controls hospitalized for other reasons were identified. The AMI cohort was classified by MI severity (severe=involving 3 arteries, left ventricle ejection fraction ≤35, CK-peak >1200 mg/dl, or CK-MB >200 mg/dl). The association of MCP with AMI severity was tested by linear and multiple regression analysis that included conventional cardiovascular risk factors, gender, age, and treatment. Associations of MCP with BMI in patients was assessed by linear correlation. In the AMI cohort, MCP correlated with four measures of AMI severity: number of vessels (β=0.382, p=0.001), ejection fraction (β=-0.315, p=0.003), CK (β=0.260, p=0.014) and CK-MB (β=0.334, p=0.001), as well as survival time (β=-0.252, p=0.031). In multivariate analysis of patients stratified by AMI severity, MCP predicted AMI severity independently of age, gender, BMI and CHD risk factors (OR=1.382, 95 % CI 1.046-1.825; p=0.023). Survival was affected mainly by AMI severity.

Conclusions: MCP is associated with adult BMI, atherosclerosis-related risk, and severity of AMI.

Keywords: cholesterol, pregnancy, developmental programming, cardiovascular disease

Introduction

Early atherogenic processes in the human aorta begin during fetal development and are accelerated by maternal hypercholesterolemia during pregnancy, even if the latter is only temporary [1,2]. Maternal hypercholesterolemia is also associated with greatly accelerated atherogenesis in normocholesterolemic children, as shown by the FELIC study [3]. In experimental models lacking the genetic and dietary variability of humans, postnatal atherosclerosis increases in proportion to the maternal cholesterol levels well into adult ages [4,5]. A molecular mechanism explaining the transfer of maternal cholesterol to the fetus has been elucidated [6], the involvement of increased oxidative stress has been established [4,5,7,8] and the beneficial effect of lowering maternal cholesterol levels before and during pregnancy by pharmacological interventions or immune modulation has been shown in preclinical models [4,5,9,10].

The absence of routine cholesterol determinations during gestation in most countries has limited investigations of the impact of elevated maternal cholesterol during pregnancy (MCP) on clinical manifestations in adult offspring. However, a recent study in patients from the Framingham Heart Study indicated that gestational hypercholesterolemia can be assumed in mothers who are hypercholesterolemic both before and after pregnancy, and that maternal dyslipidaemia is predictive of dyslipidaemia in their offspring [11]. Adults who had been exposed to elevated maternal LDL-C levels had 3.8 times higher odds of having elevated LDL-C levels, and this explained 13% of the variation in adult offspring LDL-C levels beyond common genetic variants and classic risk factors for elevated LDL-C levels [11]. A positive association has also been reported between maternal cholesterol and new-born HDL cholesterol and subclasses [12]. Furthermore, in 78 fetal aortas maternal cholesterol explained 61% of the variance of early lesion sizes in multivariate analysis independently of HDL-C, triglycerides, glucose and BMI. Maternal total cholesterol and LDLC levels were positively associated with methylation of SREBP2 in fetal aortas, suggesting a role of maternal cholesterol level during pregnancy on epigenetic signature in offspring [13]. Now we have the detailed mapping of SREBP2 methylation [14]. It remains, however, unknown whether maternal hypercholesterolemia affects the long-term progression of atherosclerosis and, more importantly, its clinical manifestations [15,16]. Establishing this would be important, because in contrast to inherited genetic risk, increased susceptibility to atherogenesis resulting from developmental programming may be prevented by brief dietary or other interventions in mothers [10]. Remarkably, in several cohort studies, whole blood DNA methylation signatures of diet are associated with cardiovascular disease risk [17]. The main aim of this retrospective study was to investigate the association between MCP and the long term effects on coronary events in their offspring.

Methods

The present study encompasses a cohort of patients from 7 hospitals in the Regione Campania (the region surrounding Naples) an area in which developmental programming of offspring cardiovascular disease in hypercholesterolemic mothers has been previously studied [13,18-20]. Between January 1991 and April 2019, 12327 patients admitted with the diagnosis of AMI were screened. To reduce potential bias in patient's selection, we restricted analysis to subjects born after World War II, because data on maternal cholesterol

before that period were scarce. For the 3357 subjects born after 1945 initially identified, we sought to obtain maternal cholesterol data from records of the hospital where the mother had undergone prenatal exams. These were obtained from the AMI patients by phone or at follow-up evaluation. In 3123 cases we were unable to obtain such data because of unavailability of maternal records (1972 cases), inaccessibility of prenatal exams (902 cases), or unwillingness of AMI patients to participate in the study (249 cases). Of the remaining 234 cases, 135 did not meet the following criteria used to define AMI: 1. typical chest pain and electrocardiographic changes with Q waves indicating transmural infarction; 2. elevated creatinine kinase concentrations, 3. availability of coronary angiography and echocardiogram. The number of AMI-patients (n=99) was further reduced by exclusion of 10 subjects with terminal ~~ill~~ness or cerebrovascular disease.

While admitted, all patients received thrombolytic therapy. Parameters collected from the patients' medical records at the time of hospitalization included: age at the time of AMI, gender, and number of major cardiovascular risk factors prior to the AMI: obesity, diabetes, smoking (past and/or present), hypertension (arterial pressure $\geq$ 140/90 mmHg), family history of CHD, family history of hypercholesterolemia, and angina at any time prior to the AMI (all assessed as "yes/no"), as well as drug treatment prior to AMI (ACE-inhibitors, beta-blockers, statins, aspirin; yes/no). Together with mean MCP obtained during the first and the second trimester of pregnancy, these parameters were considered to be potential predictors of AMI severity. The four parameters directly reflecting AMI severity were: the extent of coronary arteriosclerosis, expressed as the number of coronary arteries involved (i.e. showing greater than 75% stenosis), left ventricular function measured by echocardiography and expressed as % of normal ejection volume during the acute phase of AMI, creatinine kinase (CK) peak, and CK-MB peak. Other data obtained during initial hospitalization that may be either co-contributor or influenced by AMI severity included blood pressure, C-reactive protein (CRP), and plasma lipids (total, LDL and HDL cholesterol). The outcome of AMI was assessed as death in the coronary care unit (n=11) and length of survival during 5-year follow-up. For all 22 patients who died dur~~i~~ng the follow-up period, a cardiovascular cause of death was established from hospital records (n=17) or death certificates or a contact with the patient's cardiologist (n=4) or physician (n=1). The local ethical committee approved this study (Code.# 09/03)

Controls fell into 4 broad diagnostic groups; patients admitted for cerebrovascular conditions (n=38), surgical patients (n=90), patients admitted for infections or sepsis (n=35) and other diagnoses (n=58). However, this additional control group with such heterogeneity may be confused (i.e infection and sepsis), thus, we presented these results only as supplementary data restricting the major focus on MCP, BMI, CV risk factors and AMI severity.

Statistical methods

Data were analysed with SPSS software. Results are reported as mean ± SD. Initial analysis of the AMI group: Normal distribution of scalar parameters was assessed by Kolmogorov-Smirnov assay. All parameters were normal-distributed, except BMI, CRP, SSA and diastolic BP. Log-transformation improved CRP normality and slightly improved that of BMI, but not diastolic BP, which was therefore excluded from further analysis. The association between MCP (independent parameter) and age, measures of AMI severity, and 5-year survival (dependent parameters) was determined by linear regression analysis. To assess which

parameters determine the severity of AMI and survival, patients were stratified into severe and non severe. Severe AMI was defined as meeting at least one of the following criteria: Left ventricle ejection fraction ≤ 35%, CK-peak > 1200 mg/dl, CK-MB peak > 200 mg/dl, presence of 3 vessel disease [18-20] Differences between the resulting two severity groups in categorical parameters, i.e. gender, diabetes, hypertension, obesity (BMI ≥ 30), previous angina, familiar history of coronary heart disease, familiar history of hypercholesterolemia, therapy (ACE-inhibitor, beta blockers, statin and aspirin), in hospital death, death at follow-up, and overall mortality were established by Chi-square analyses. Differences in scalar parameters, i.e. age, MCP, patients' total, LDL and HDL cholesterol and triglycerides after the AMI, BMI, CPR, systolic blood pressure, left ventricle ejection fraction, CK-peak, CK-MB peak, and the number of vessels with lesions causing > 75% stenosis, were evaluated by one-way ANOVA. Logistic regression analysis was used to evaluate the association of maternal cholesterol with dichotomous AMI severity, including gender, age, BMI, number of risk factors and total cholesterol measured soon after hospitalization as covariates. For this purpose, MCP was stratified by 10 mg/dl increments. Cox regression analysis was used to evaluate the independent effect on overall mortality of gender, age, MCP, BMI and number of risk factors. $P < 0.05$ was considered significant. Comparisons between AMI and control groups were done by ANOVA and unpaired T-test. Correlations between parameters in pooled data of all AMI and control subjects were assessed by pairwise Pearson's two-tailed linear correlation or for scalar parameters, by linear correlation and linear regression analysis.

RESULTS

The initial population of AMI patients are characterized in **Table 1**. As expected, the vast majority of the 89 patients suffering AMI at relatively young age (47.0±5.0 years) were male (84.3%).The frequency of MCP in a normal maternal population is that 72.3% of mothers met the definition of hypercholesterolemia in current guidelines (MCP >240 mg/dl) [21]. We first examined the correlation between MCP and the age at which the AMI occurred, several measures of AMI severity, and other scalar parameters unaffected by the severity of the AMI, using linear regression analysis (**Table 2**). MCP showed no significant correlation with age. In contrast, there were strong correlations with all four measures of AMI severity, i.e. the number of coronary arteries involved (β= 0.382, p=0.001) (**Figure 1A),** the reduction of left ventricle ejection fraction (β= -0.315, p=0.003) (**Figure 1B**), the CK-MB peak (β= 0.334, p=0.001) (**Figure 1C**), and the CK peak (β= 0.260, p=0.014) (**Figure 1D**). No correlation was found between MCP and the number of risk factors, but BMI showed a strong positive correlation (β= 0.845, p=0.001) (**Table 2**).

MCP also correlated with some parameters measured shortly after the AMI**:** total plasma cholesterol (β= 0.373, p=0.001), log-transformed CRP (β= 0.248, p=0.020), but not systolic blood pressure (β= -0.138, p=0.196), HDL-C (β= -0.017, p=0.880), or triglycerides (β= -0.041, p=0.700). However, these associations are less meaningful, because they may reflect the effect of AMI severity on post-AMI measurements rather than a direct effect of MCP.

To test the effect of MCP on AMI in the presence of cofactors, a composite measure of AMI severity was used. Patients classified as having severe AMI (3 vessel disease, left ventricle ejection fraction ≤ 35%,

CK-peak > 1200 mg/dl, or CK-MB > 200 mg/dl) were significantly worse in all 4 original measures of AMI severity than patients with less severe AMI (**Table 3).** The two groups were then compared (**Table 4**). The 33 subjects with severe AMI were younger and had higher MCP. They also had more risk factors and were more obese. No differences were observed in smoking habits, previous angina, CHD history, dyslipidemias and diabetes. The treatment with ACE-inhibitors, beta-blockers, statins, and acetylsalicylic acid was similar. In-hospital deaths, mortality during the 5 years follow up period and overall mortality were higher in subjects with severe AMI **(Table 3)**.

Variables included in the analysis were those statistically different in univariate analysis, except for gender, which was included because of the clinical relevance of gender in adult AMI. BMI was included because obesity was retained as independent variable for the association found in univariate analysis but not considered in the joint variable "Risk Factors". Logistic regression analysis demonstrated that maternal cholesterol during pregnancy predicts the occurrence of severe AMI (OR=1.382, 95 % CI=1.046-1.825; p=0.023) independently of the effect of age, gender, BMI and number of risk factors (OR=1.669, 95 % CI=1.099 - 2.534, p=0.016) and total-C (**Suppl. Table 1)**.

Linear correlation between MCP and length of survival indicated a significant correlation (β= -0.232, p=0.031) (**Table 2**). We therefore used Cox regression analysis to further explore this, but only the severity of AMI predicted mortality independently of the effect of age, gender, number of risk factors, and MCP (HR=2.619; 95% CI 1.030-6.659, p=0.043) **(Figure 2 and Suppl. Table 2)**.

Controls and AMI groups had similar average MCP values, even though significant differences were evident in several risk factors.

Because no measurements of atherosclerosis were available for most control cases, we used two surrogate parameters to determine whether MCP is associated with increased cardiovascular risk in adults. The first consisted of the number of classical risk factors, the second was the number of classical risk factors plus the presence of clinical manifestations, such as AMI or cerebrovascular disease. When pooled data of all 310 AMI and control cases were analysed together, MCP was correlated with both measures of atherosclerosis risk in pairwise linear correlation (p<0.001) (**Table 5**) as well as in multivariate analysis with age, gender, and all risk factors as covariates (β= -0.060, p=0.021).

Discussion

The present study established that: 1) increased MCP was associated with greater severity of AMI; 2) in multiple regression analysis of patients stratified by a composite measure of AMI severity, the association of MCP with AMI severity was independent of classical CHD risk factors, including gender; and 3) MCP showed a remarkably strong association with the BMI of patients. .The association between MCP and AMI severity is remarkable, considering it was established in a small study population, and because variability in genetic, dietary, and other risk factors may have confounded the effects of developmental programming. Given that MCP markedly increases atherogenesis in human fetuses and children [1-5,13,14] and adult offspring of experimental animals [4,9,22-24], one would expect MCP to be associated with more extensive atherosclerosis, and more extensive atherosclerosis with a greater likelihood of plaque rupture and

AMI. Based on similar MCP levels, one would assume that AMI patients and controls had similar extent of atherosclerosis. Furthermore, linear regression analysis of pooled data from all 310 subjects indicated a significant association between MCP and two cumulative measures of atherosclerosis risk, consistent with an atherogenic effect of increased MCP. Thus, MCP may play a significant role in atherogenesis, but not in the likelihood of a transition from atherosclerosis to the coronary events.

Overall, the present results establish in a well characterized human population that the effects of developmental programming by MCP persist well into adult age, and that they affect a clinically relevant outcome, i.e. the severity of AMI. Our study does not, however, permit estimates of how much MCP contributed to the severity of AMI, nor does it establish causality. Evidence for causality has been provided by studies in preclinical models demonstrating that interventions which reduce MCP, decrease oxidative stress associated with gestational hypercholesterolemia, or enhance active immune defences against oxidative stress in offspring protect against developmental programming by MCP.

The main limitations of our study are the small number of cases resulting from the exclusion of older adults, which constitute the bulk of the AMI patients, and the lack of data on maternal dietary and lifestyle confounders. In contrast to the FELIC study [3], where MCP measurements dating back 1-14 years could be retrieved, going back up to 65 years proved challenging. We cannot rule out that the correlation between MCP and patients' BMI is influenced by inclusion of mothers whose hypercholesterolemia is associated with genetic predisposal to obesity and/or metabolic disorders. Second, our study is subject to all the limitations of a retrospective study, in particular the lack of information on many maternal and/or paternal transgenerational effects, such as dietary and lifestyle habits. Moreover, for the majority of patients included only first and second trimester MCP data were available. Mean MCP for all subjects were calculated only from these time points. However, cholesterol levels are known to increase in the third trimester in many women. Our study was therefore largely blind to the effects of temporary hypercholesterolemia during pregnancy. Mothers with temporary hypercholesterolemia may have relatively modestly elevated MCP in early pregnancy, yet their offspring are clearly subject to atherogenic programming [1,25]. Similarly, data reflecting only the first two trimesters may underestimate the true difference in MCP between AMI and control mothers.In view of the increasing recognition of the importance of developmental programming, prospective trials are clearly necessary to avoid these weaknesses and to further establish the role of MCP and other gestational factors on adult diseases.

Nevertheless, we believe that MCP is not only an important risk factor for childhood atherogenesis, but also for the severity of AMI in young adults. This suggests that MCP should be included among risk factors prompting more intensive screening and primary prevention in high-risk children.

Acknowledgements: We dedicate this paper to the memory of Dr. Antonio Liguori (1944-2018). Supported by Italian Ministry of Health Progetto di Ricerca Finalizzata 2007-2009 (FC), National Institutes of Health grants HL067792 and HL089559 (WP and CN), Progetto di Rilevanza Nazionale of Italian Ministry of

University and Research PRIN 2017 (CN), and Ellison Medical Foundation Senior Scholar Award 1851-07 (WP).

Author Contributions:Contribution to the manuscript. FC, WP and CN contributed to the conception or design of the work. GB and GR contributed to the acquisition, of data for the work. FC, PA, WP contributed to statistical analysis. FC, WP and CN contributed to interpretation. FC, WP, CN drafted and critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy. None of the authors declared a conflict of interest.

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Table 1: Clinical Characteristics and main outcomes of the AMI Group.

Parameter	
Number of patients	89 (75 males, 14 females)
Age (years; range)	47.0 ± 5.0 (36 - 56)
Maternal cholesterol during pregnancy (mg/dl; range)	268.8 ± 37.9 (177 - 356)
"Normal" [< 240 mg/dl] (n; %)	22 (24.7 %)
"High" [≥ 240 mg/dl] (n; %)	67 (75.3 %)
Cardiovascular risk factors:	
Obesity [BMI > 30] (n; %)	30 (33.7 %)
Smoking [past and/or present] (n; %)	54 (60.7 %)
Hypertension [≥140/90 mmHg] (n; %)	27 (30.3 %)
Family history of CHD (n; %)	48 (53.9 %)
Diabetes (n; %)	19 (21.3 %)
Family history of hypercholesterolemia (n; %)	23 (25.8 %)
Prior angina (n; %)	39 (43.8 %)
Number of risk factors (n; range)	2.7 ± 1.5 (0 - 7)
Drug treatment prior to AMI:	
ACE-inhibitors (n; %)	14 (15.7 %)
Beta-blockers (n; %)	11 (12.4 %)
Statins (n; %)	8 (9.0 %)
Aspirin(n; %)	23 (25.8 %)
AMI location:	
Left anterior descending (n)	37
Circumflex (n)	44
Right anterior (n)	8
Parameters of AMI severity:	
Number of coronaries with >75% stenosis involved (n; range)	1.82 ± 0.67 (1 - 3)
Left ventricle ejection fraction during AMI (%; range)	44.17 ± 6.14 (30 - 56)
CK peak (IU; range)	1085.6 ± 240.5 (665 - 1678)
CK-MB peak (IU; range)	146.0 ± 67.5 (56 - 306)
Laboratory parameters in hospital, after AMI:	
Blood pressure, systolic (mm HG)	101.0 ± 10.4
C-reactive protein (mg/l)	5.45 ± 2.66
Total plasma cholesterol (mg/dl)	208.9 ± 27.5
LDL cholesterol, calculated (mg/dl)	131.6 ± 26.5
HDL cholesterol (mg/dl)	39.4 ± 4.3
Triglycerides (mg/dl)	189.6 ± 2.7
Outcome:	
In-hospital death (n)	11 (12.4 %)
Death during 5-year follow-up (n; %)	22 (24.7 %)
Alive after 5 years (n; %)	56 (62.9 %)
Survival length of all 83 patients (months)	46.5 ± 21.3

Table 2: Linear Correlations Between MCP, age at Myocardial Infarction (AMI), AMI Severity, and risk factors.

Dependent variable	Beta Coefficient	P
Age	- 0.088	0.412
Number of vessels involved	0.382	0.000
Left ventricle ejection fraction	- 0.315	0.003
CK peak	0.260	0.014
CK-MB peak	0.334	0.001
Number of risk factors	0.251	0.271
BMI (log-transformed)	0.845	0.000
Survival	- 0.232	0.031

Table 3: Patient stratification by AMI Severity.

Variables	Severe AMI		
	No (n=56)	**Yes** (n=33)	**P**
Number of vessels affected	1.6 ± 0.5	2.3 ± 0.7	0.000
Left ventricle ejection fraction	46.2 ± 5.4	40.8 ± 6.2	0.000
CK peak	943.9 ± 134.6	1325.9 ± 181.0	0.000
MB peak	107.0 ± 33.7	211.7 ± 59.7	0.000

Table 4: MCP, age, CV Risk Factors, and treatments of AMI patients.

Variables	Severe AMI		P
	No (n=56)	**Yes** (n=33)	
Maternal cholesterol	255.3 ± 35.3	283.9 ± 40.7	0.001
Obesity (%)	16.1	63.6	0.000
Smoking (%)	58.9	63.6	0.417
Hypertension (%)	23.2	42.2	0.049
Angina (%)	42.9	45.5	0.492
CHD History (%)	53.6	54.5	0.553
TC History (%)	17.9	39.4	0.024
Diabetes (%)	17.9	27.3	0.217
Number of risk factors (n)	2.3 ± 1.2	3.4 ± 1.8	0.001
ACE inhibitor (%)	17.9	12.1	0.345
Beta-blocker (%)	12.5	12.1	0.618
Statins (%)	8.9	9.1	0.629
Aspirin (%)	28.6	21.2	0.306
In-hospital Death (%)	7.1	21.2	0.055
Deaths during follow-up (%)	14.3	42.4	0.004
Death (%)	21.4	63.6	0.000

Table 5: Association of MCP and current BMI with patient characteristics.

	MCP	BMI
Age	0.38	0.64
Gender	0.30	0.40
MCP	-	0.000
BMI	0.000	-
Smoking	0.61	0.037
Family history of CHD	0.22	0.70
Diabetes	0.30	0.011
Family history of hypercholesterolemia	0.062	0.015*
Angina	0.156	0.276
Number of classical risk factors	0.000	0.000
Number of atherosclerosis-related risk factors	0.000	0.000

*p< 0.05 - Pearson's correlation; 2-tailed significance

Table 1, Suppl. AMI Group: Logistic Regression Analysis Assessing the Effect of Maternal Cholesterol During Pregnancy on AMI Severity in the Presence of Covariates Age, Sex, total cholesterol, BMI and Number of Risk Factors.

Variables	Odds ratio	95 % confidence interval	P
Age	0.983	0.876 - 1.104	0.777
Gender	0.714	0.133 - 3.822	0.694
Risk Factors	1.669	1.099 - 2.534	0.016
Maternal Cholesterol (10 mg)	1.382	1.046 - 1.825	0.023
Total Cholesterol	1.001	0.981-1.022	0.904
BMI	1.116	0.795-1.588	0.526

Table 2, Suppl AMI Group: Cox Regression Analysis Assessing the Effect of AMI Severity on Overall Mortality in the Presence of Covariates Age, Sex, BMI, Risk Factors and Maternal Cholesterol.

Variables	Hazard ratio	95 % confidence interval	P
Age	0.980	0.907 - 1.059	0.616
Gender	0.930	0.302 – 2.866	0.899
Risk factors	1.243	0.952-1.625	0.110
Severe AMI	2.619	1.030 - 6.659	0.043
BMI	1.189	0.970-1457	0.096
Maternal Cholesterol (10 mg)	1.041	0.937 - 1.157	0.451

Table 3, , Suppl. Characterization of AMI and Control Patients.

Parameter	AMI patients	Cerebro-vascular Controls	Surgical controls	Infection / sepsis controls	Other Controls	All controls	All subjects
Number (n)	89	38	90	35	58	221	310
Gender (n)	75m, 14f	30m, 8f	72m, 18f	32m, 3f	50m, 8f	184m, 37f	259m, 51f
Age (years)	47.0 ± 5.0	47.0 ± 4.7	47.0 ± 5.0	46.0 ± 5.5	47.3 ± 5.4	46.7 ± 5.1	46.8 ± 5.1
MCP (mg/dl)	269 ± 37.9	267 ± 44.3	272 ± 34.3	277 ± 38.2	272 ± 41.9	270 ± 39.0	270 ± 40
BMI	28.0 ± 2.6	28.2 ± 2.7	27.8 ± 2.5	27.3 ± 2.7	28.2±2.6	27.9 ± 2.6	27.9 ± 2.6
Smoking (%)	61	39*	44*	43	53	46*	50
Family history of CHD (%)	54	29*	37*	11*	36*	31*	38
Diabetes (%)	21	13	19	11	5*	13	15
Family history of hyper-cholesterolemia (%)	26	26	28	14	17	23	24
Prior angina (%)	44	44*	24	33	26	34*	35
Number of risk factors:							
Classical (n)	2.34 ± 1.31	1.63 ± 1.34*	1.89 ± 1.35*	1.26 ± 1.10*	1.71 ± 1.12*	1.43 ± 1.08*	1.88 ± 1.31
Atherosclerosis-related (n)	3.34 ± 1.31	2.63 ± 1.34*	1.89 ± 1.35*	1.26 ± 1.10*	1.71 ± 1.12*	1.61 ± 1.13*	1.88 ± 1.31
Drug treatment:							
ACE-inhibitors (%)	16	18	19	17	9	16	16
Beta-blockers (%)	12	18	17	9	16	15	15
Statins (%)	9	13	13	17	29*	18	15
Aspirin (%)	26	24	32	11*	33	28	27

The number of atherosclerosis-related risk factors equals the number of classical cardiovascular risk factors plus 1 for cardiovascular disease manifestations (AMI or cerebrovascular)
** significant v.s. AMI group at P≤ 0.05 or less*

Figure Legends

Figure 1. Correlation between maternal cholesterol during pregnancy and AMI severity, i.e. the number of coronary arteries involved (**A),** the reduction of left ventricle ejection fraction (**B**), the CK-MB peak (**C**), and the CK peak (**D**).

Figure 2. Cox regression analysis of AMI severity and 5-year survival.

Figure 3. Correlation of maternal cholesterol during pregnancy with BMI in the study population.

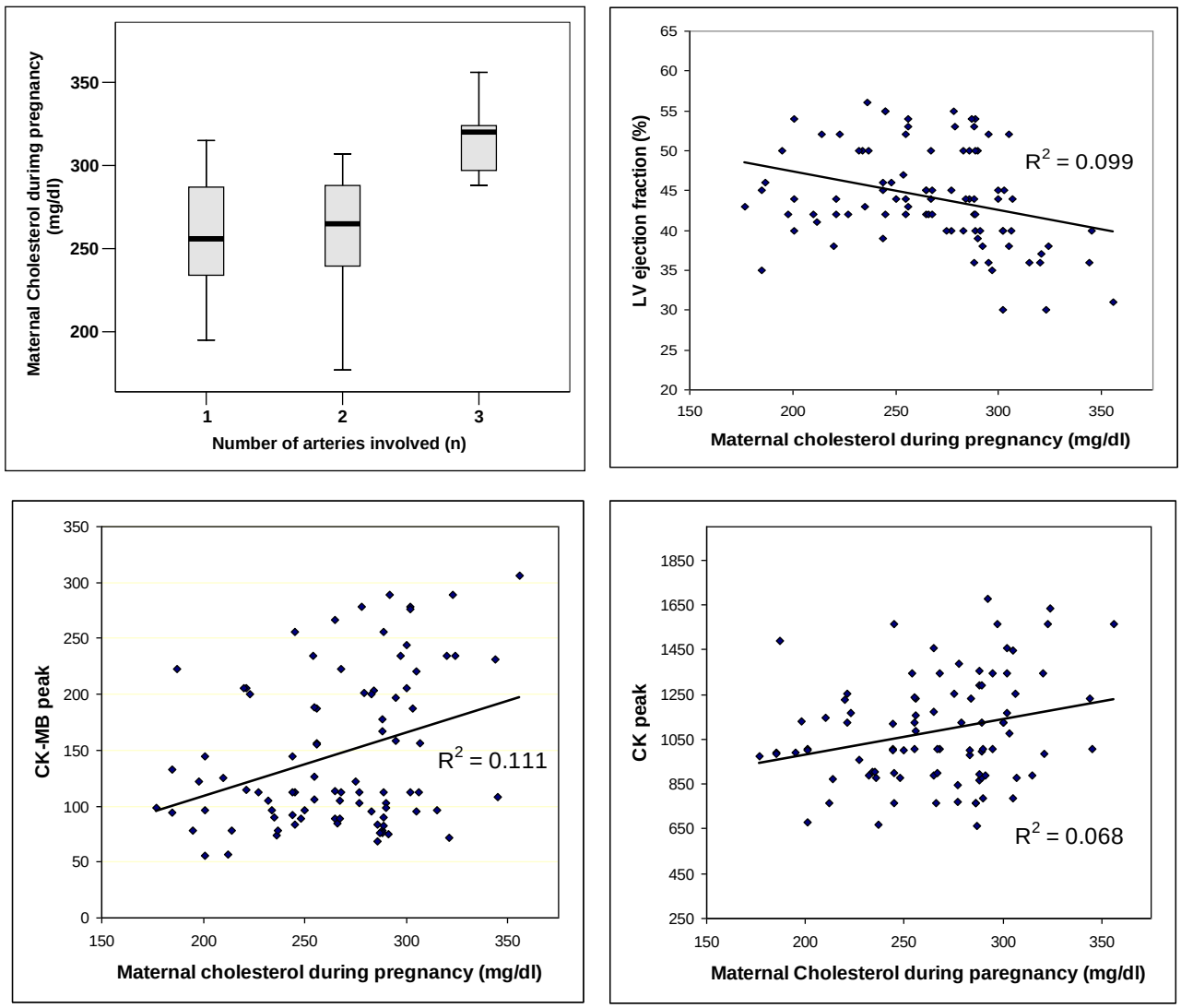
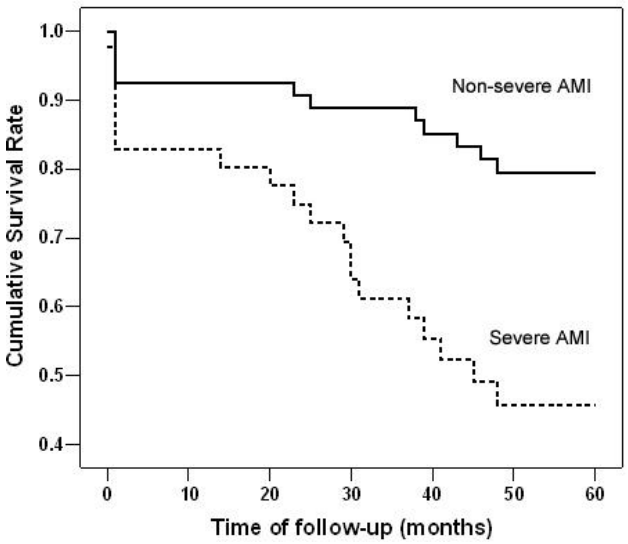

Maternal Cholesterol durimg pregnancy (mg/dl)
350
300
250
200
1
2
3
Number of arteries involved (n)
LV ejection fraction (%)
65
60
55
50
45
40
35
30
25
20
150
200
250
300
350
R2 = 0.099
Maternal cholesterol during pregnancy (mg/dl)
CK-MB peak
350
300
250
200
150
100
50
0
150
200
250
300
350
R2 = 0.111
Maternal cholesterol during pregnancy (mg/dl)
CK peak
1850
1650
1450
1250
1050
850
650
450
250
150
200
250
300
350
R2 = 0.068
Maternal Cholesterol during paregnancy (mg/dl)

Fig 1

Fig 2.


Cumulative Survival Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
Non-severe AMI
Severe AMI
0
10
20
30
40
50
60
Time of follow-up (months)

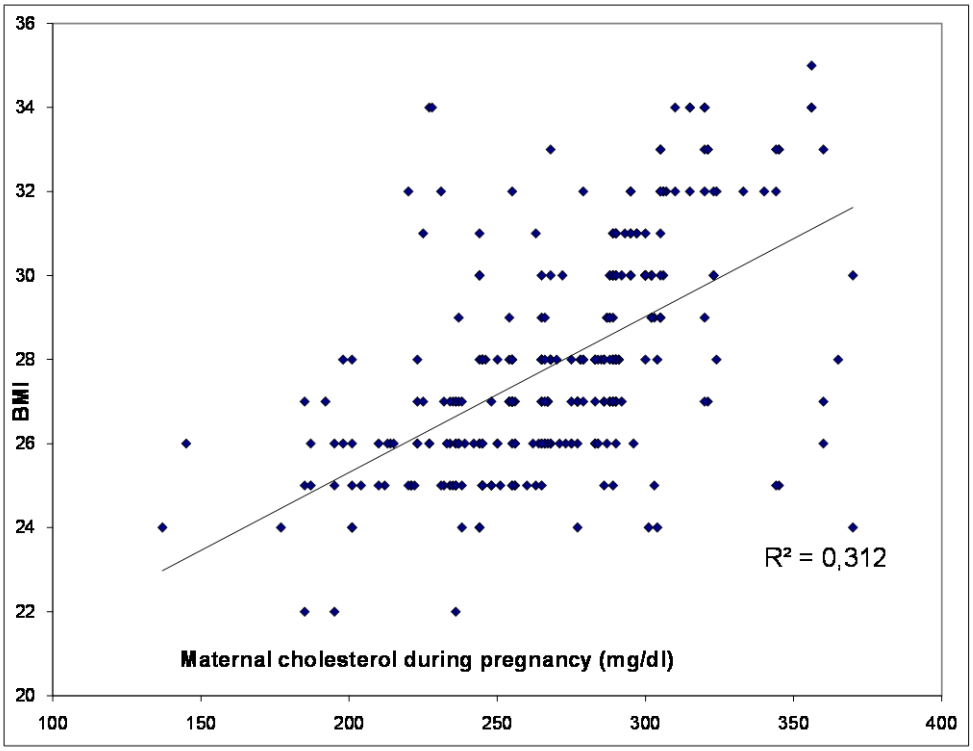

BMI
Maternal cholesterol during pregnancy (mg/dl)
R² = 0,312
36
34
32
30
28
26
24
22
20
100
150
200
250
300
350
400

Fig. 3.

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