Gender, reproductive ageing, adiposity, fat distribution and cardiovascular risk factors in Spanish women aged 45-65.

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Abstract:

Recent results on cardiovascular diseases (CVD), cardiovascular risk factors (CVRF) and THS as a protective factor for CVD in middle aged and elderly women are changing traditional ideas, rising new interest in the ways in which sex and gender interact with environmental and cultural contexts and demanding more research on health with a gender approach. In this paper, besides age, menopausal status and adiposity markers, five different hormonal markers of reproductive ageing have been used to predict variation in CVRF (cholesterol, triglycerides, glucose, systolic and diastolic blood pressure), in a sample of 988 pre- and naturally postmenopausal Spanish women, aged 45-64 years. Adiposity, fat distribution and weight change explain a significant part of the variability founded in CVRF. Our main conclusions are: a). Women who smoke have significantly more elevated triglycerides compared with non-smokers. B) Menopausal status is not predictive of any cardiovascular risk factor after adjusting for age. C) Weight change through reproductive age may be an important mediator of the observed increase of cardiovascular risk factors with age and with menopause, since age at menopause has been show to increase with total adiposity, and increased weight change during reproductive life. More elaborated gender approaches are needed to explain the differences in medical perception of CV risk, of CV disease, for different diagnosis and treatment, and to understand the extensive use of hormone therapy for CVD prevention, despite recurrent evidences on its negative effects precisely on Heart disease

Key words: Gender, reproductive aging, menopause, triglycerides, weight change.

Cardiovascular disease, is now days the leading cause of death for men and women both for developed and developing countries (Mackay and Mensah, 2004); For men and women, cardiovascular risk is known to increase with age, smoking, hypertension, blood lipid glucose levels, and central obesity (Beck-Nielsen, 1990; Klag *et al*., 1993; WHO, 2003). Despite that over the lifespan, approximately the same proportion of the female population as the male population dies of complications resulting from CVD, it has been traditionally considered as a middle-age "male" disease , the consequence has been for long, the exclusion of women from clinical trial and epidemiological studies, making extensive to women the results obtained for men. In the 1970s, it was suggested that endogenous hormones protect against CVD in women, and that oestrogen deprivation after menopause increased their cardiovascular risk (Kannel *et al.*, 1978). Since then, much has been published about the role of menopause in differential cardiovascular risk and about the mechanisms to explain why menopause is a risk factor for cardiovascular disease. These were mainly based on studies of the administration of exogenous estrogens, including combinations (Stampfer & Colditz, 1991; Psaty *et al.*, 1993; WHO, 1996; Kannel & Wilson, 1995; Paganini-Hill 2002), but recent randomised studies, including mainly elderly women on primary or secondary prevention, could not confirm this protective effect of a single combined regimen (Consensus Development Conference, 2003).

Consistent evidence demonstrating that menopause is significantly associated with earlier or more pronounced onset of cardiovascular disease in woman was controversial in late nineties, (Sowers, 1996; Sowers & La Pietra, 1995; Rueda, 1998).

It has been traditionally argued that in addition to the effect of aging, menopause and endogenous sex hormones are strongly associated with cardiovascular risk factors around the time of menopause (Shelley *et al.*, 1998; Portaluppi *et al.*, 1996), through lipid modifications, (Bonithon-Kopp *et al.*, 1990; Jensen et al 1990; Steevenson et al, 1993; Hall et al, 2002). Whereas no consistent association has been found between menopause and other risk factors for cardiovascular diseases such as blood pressure or obesity, large prevention trials not only failed to confirm this protective effects (Staren & Omer, 2004, Lancet 2003; Hulley et al 1998), but indicate that oral estrogens increases the risk of venous trombo-embolism (Oger y Scarabin, 1999).

The metabolic syndrome, which encompasses a range of conditions known to be CVD risk factors, (Jacobson et al, 2004) also, has a greater impact on the incidence of CVD in women than in men.

Elevated triglyceride levels, and diabetes, have more of an impact on the risk picture for women than for men, especially in middle age, (Doteval et al, 2004)

On the other hand, other results suggest that age and adiposity (measured through BMI), may be as important in determining the lipoprotein pattern and blood pressures as menopausal status (Wu *et al.*, 1990; Matthews *et al.*, 1994; Pasquali *et al.*, 1994 Sowers & La Pietra, 1995; WHO, 1996;Portaluppi *et al.*, 1997; Hall *et al.* 2002).

In a previous paper, we explored the interaction between age, reproductive ageing and adiposity, (Custodio *et al.*, 2003); our results showed that variation in cholesterol and ferritin is better explained by reproductive ageing, while that in glucose and triglycerides is better explained by changes in total and visceral adiposity. In this paper, besides age, menopausal status and adiposity markers, five different hormonal markers of reproductive ageing (FSH, LH, estradiol 17B, estrone and androstenedione) have been used to predict variation in CVRF (cholesterol, triglycerides, glucose, systolic and diastolic blood pressure) in a sample of 988 pre- and naturally postmenopausal Spanish women, aged 45-64 years. The objectives are:

a) To explore the relationship between the markers of reproductive ageing and cardiovascular risk factors, taking into account chronological age and adiposity indicators.
b) To determine to what extent adiposity, fat distribution and weight change are independent predictors of cardiovascular risk factors.
c) To explore whether the effects of menopause on CVRFs, can be mediated by adiposity, fat distribution and weight change, which are known to affect the process of reproductive ageing, including the age at menopause.
d) To show how biological anthropologists can contribute to the understanding of he origins of the differences in health experiences between men and women, focusing on gender for explaining both sex differences, and interaction between biology and culture. Gender approach explains differences for medical perception of risk, real differences in risk and disease, different diagnosis and treatment.

Material and methods

A cross-sectional sample of 998 women aged 45-65 years, both pre- and naturally postmenopausal (51.4%) from a deprived socioeconomic stratum was analysed. All women lived in Alcobendas, Madrid. They participate in a preventive gynaecological health programme jointly run by the Health Councils of Alcobendas Town Council and of the Autonomous Government of Madrid, with the participation of the Anthropological Unit of the Universidad Autónoma de Madrid.

Between 1996 and 2000, all women from Alcobendas in the age range 45-65 years were invited to participate in the health program; all participants in the research program gave their signed, informed consent. Gynaecological examination, cytology, ovarian echography and mammography were performed in the Cantoblanco Hospital, where women were taken free of charge by municipal bus. Anthropometry and detailed surveys of socioeconomic characteristics, lifestyle, menstrual and reproductive history, and a 24-hour food recall were performed by trained members of the research team. Height, setting height (Harpender anthropometer) and weight, were measured to the nearest 0.1cm and 0.5 kg, respectively. Minimum waist and maximum hip circumference were measured to the nearest 0.1. Blood pressure (seated) was measured twice in each woman using a mercury sphygmomanometer, and the mean calculated.

Fasting blood samples were taken between 0830 and 0930 in the Cantoblanco Hospital (Madrid). All blood samples from premenopausal women were obtained between days 18 and 22 of their menstrual cycle. FSH, LH, E2, P, cholesterol, triglycerides and glucose were tested in 744 women. E1, androstenedione (T4-A) and growth hormone were tested in 244 frozen blood samples, randomly chosen to represent the proportion of pre-, peri- and postmenopausal women in the sample. Cholesterol, triglycerides and glucose levels were assessed using a Hitachi 717 chemical analyser. Total plasma cholesterol and triglycerides were evaluated using the TWIN Triglycerides GPO-PAP/Cholesterol CHOD/PAP enzymometric test (Roche Diagnostics GMBH, Mannheim, Germany). Glucose was determined using the hexokinase Gluco-quant Glucose/HK method (Roche Diagnostics GMBH, Mannheim). Plasma levels of FSH and LH were assessed by the AIA-PACk FER immunoenzymometric test (Toso Corporation, Tokyo, Japan).

The following variables were used to measure reproductive ageing: plasma levels of FSH, LH, E2, E1, T4-A, and menopausal status: premenopause: less than 12 months after last menstruation; postmenopause: 12 months or more after last menstruation. More detailed methodological and sample information can be found in Custodio (2002), Barroso (2003) and Bernis *et al.* (2003).

Separate multiple linear regressions were calculated for each of the five cardiovascular risk factors (total cholesterol, glucose, triglycerides, systolic and diastolic blood pressure) with respect to the explanatory capacity of the four groups of variables (age, reproductive ageing, adiposity, fat distribution and weight change, and smoking) summarised in Table 2.

A one-way ANOVA (GLM) was carried out for each of the five CVRFs, using the variables found to be of predictive value from the multiple regression models. For all CVRFs, age (age groups: 45-49, 50-54, 55-59 and 60-64) and weight change (no change or weight loss, 1-8 Kg increase, 9-21

kg, more than 21 kg increase) were introduced as factors, variables with predictive value from regression models were introduced as covariables.

Results

Table 1 summarises the basic information on the gonadotrophic, ovarian, and extra ovarian hormones used as indicators of reproductive ageing in the analysis, classified by age group. Table 2 summarises the basic statistics for cardiovascular risk factors and adiposity indicators by age group; the F statistics and p-value from the one-way ANOVA carried out to compare mean values of different age groups are shown. All cardiovascular risk factors and adiposity indicators showed a significant increase with age.

Table 3 summarises partial correlations coefficients, (age constant), between cardiovascular risk factors. Cardiovascular risk factors were quite independent of each other. Cholesterol is the only CVRF which correlates positively and significantly with all indicators of reproductive ageing used in the analysis, except androstenedione (A4-T). None of the other CVRFs correlated significantly with hormonal markers.

Table 4 summarises partial correlation coefficients (age constant), between each cardiovascular risk factor and the markers of adiposity, fat distribution, and weight change. All cardiovascular risk factors correlated positively with the markers of total fat, fat distribution, and weight change, apart from cholesterol, which was not correlated with adiposity in any case.

Table 5 shows the results of the five multiple stepwise regression analyses after accounting for age and menopausal status, which were performed to test: 1) the relative contribution of reproductive ageing after removing the effects of age, 2) the effects of adiposity, fat distribution and weight change after removing the effects of general and reproductive ageing. Our results show that the predictive variables included in the models explained a small but significant part of the total variance of the cardiovascular risk factors (from 6% for glucose, to 20% for triglycerides). Cholesterol seems to be more closely associated with reproductive ageing than the other CVRFs, as shown by the significant partial correlation coefficients for gonadotrophic, ovarian and extra-ovarian hormones, and by the fact that the variation in cholesterol is predicted only by age and FSH. There was no significant relationship between estradiol, FSH, LH, estrone or androstenedione with triglyceride, SBP, DBP or glycaemia

Cardiovascular risk factors other than cholesterol are all predicted by age and weight change during reproductive life, while fat indicators behaved differently for triglycerides and total fat (BMI). As

for smoking, women who smoke have significantly elevated triglycerides. Menopausal status is not predictive of any cardiovascular risk factor after adjusting for age.

Figures 1 and 2 have been obtained in the first two GLM analysis shown in table 5; representing respectively, the variability of cholesterol and triglyceride levels with age and weight change through reproductive life. Women who do not change weight or who lose weight during reproductive life, have significantly lower values of blood lipids. It is of particular note that these women exhibit no significant change of CVRF with age. Women who put on more than 20 kg have the highest values for CVRF, and show a pronounced and significant increase in CVRF with age

Discussion

In Spain, as in other Western countries, despite the favourable trend of recent years, cardiovascular diseases are still the main cause of death (in 1992, they represented 46.7% of all female deaths, of which 34.4% were due to cerebrovascular causes, and 20.5% were due to stroke**).** Women who develop CVD in middle age generally have higher overall risk factors than men do (ie, multiple risk factors, such as those associated with the metabolic syndrome). Factors of the metabolic syndrome, including diabetes, hypertension, and hyperlipidemia, are also more prevalent in women with heart disease than in healthy women or in men with heart disease. Overt diabetes is associated with greater increase in risk for atherosclerosis in women than in men. This effect may be because of the relatively more severe dyslipidemia seen in women with diabetes compared with men with diabetes, particularly on triglyceride levels. Triglycerides correlate significantly and positively with BMI, weight change, sub scapular along reproductive life fat fold, and waist and hip circumferences along reproductive life. Also women who smoke have significantly more elevated triglycerides, in agreement with other authors (Shelley et al, 1999).

Cardiovascular risk profile of women in our sample is shown in table. Prevalence is higher than in other Spanish samples (Banegas *et al.*, 1993, 1995; Ministerio de Sanidad y Consumo, 1995). Most of these women were born and grew up in rural areas, between 1934 and 1950, coinciding with the very harsh times of the Spanish Civil War, World War II, and both post-war periods (e.g., it was only in 1960 that the mean per capita calorie consumption reached 1800 Kcal in Spain (Graciani *et al.*, 1996). Living conditions significantly improved, coinciding with their migration to Madrid, and with marriage, even though they still belonged to a low socioeconomic group. On average, they put on 15 kg during their reproductive life, this increase being inversely correlated with their pre reproductive BMI: slimmer women gained significantly more weight than stockier women (Montero *et al.*, 2000).

Our results suggest that cholesterol is more related to reproductive aging and that the other cardiovascular risk factors are more related to adiposity, changes in adiposity and fat distribution, supporting the idea that "classic" risk factors are relatively independent of each other and that population variability could be explained by different set of factors (Stevenson, 1998).
Our results agree with other authors, who have demonstrated overall that both total adiposity (measured by BMI) and visceral fat (measured either by waist circumference, waist/hip ratio, or suprailiac fat-fold), significantly increase CVRFs (Hartz *et al*, 1984; Ishida *et al*., 1997; Larsson 1984; van Pelt *et al.*, 2001); Triglycerides also increased with BMI, and interestingly, show higher levels among smokers. The novelty of our results is that weight change during reproductive life is an independent factor, that interacts with age in predicting the levels of cardiovascular risk factors.
Recent results have shown that both, for menopausal and fertile women, diet and exercise induced a significant reduction of BMI, SBP, waist circumference, ratio T. Chol/HDL-C, and apoB (Santos, 2003). In addition, lifestyle changes and pharmacological lipid-lowering therapy have shown to favourably influence the natural course of atherosclerotic disease and reduce cardiovascular events in men and women (Bittner 2002).

Conclusions.

Considering our results and the following facts, it would seem wise to follow the WHO's (2003) advice: "(...) drug therapy should be considered only after serious attempts have been made to modify diet. Intervention trials have shown that reduction of blood pressure by 6 mm Hg reduces the risk of stroke by 40% and of heart attack by 15%, and that a 10% reduction in blood cholesterol concentration will reduce the risk of coronary heart disease by 30%".

1- Despite men and women share the same CV risk factors, they have differential exposure to them (Pollard, 1999)
2- The same exposure to a risk factor is more dangerous for women, for example, tobacco use has been shown to be more dangerous for women of all ages,
3- High blood triglycerides and blood pressure increases risk of atherosclerosis more in young women, compared to young men.
4- The same symptoms in men and women have been differently diagnosed and treated by medical doctors;
5- Menopause itself has not a direct effect on CVD, (McKay & Mensah, 2004)

6- weight control through diet and exercise is demonstrably very effective in reducing all CVR- factors (WHO, 2003),
7- epidemiological evidence for any cardioprotective effect of HRT is lacking (Consensus Development Conference, 2003)
8- Epidemiological evidence demonstrates that oral estrogens increases the risk of venous tromboembolism (Oger y Scarabin, 1999; McKay & Mensah, 2004; Canonico et al, 2006).

Our main conclusion is that weight change through reproductive age may be an important mediator of the observed increase of cardiovascular risk factors with age and with menopause, since age at menopause has been show to increase with total adiposity, and increased weight change during reproductive life. Lebrun et al, 2006, conclude that in elderly and late postmenopausal women, hormonal factors do not predict quality of life, results which also point out in this direction.

Extensive medicalization of women using RTH, is a good example of how normal biological functions for the female (such as menopause) are treated as a medical problem, disease-state, or risk factor for disease. This illustrates the necessity of focusing on the role of gender and the social construction of illness, as usually diagnosis and subsequent treatments for CVD have generally favoured men, but which have rarely advantaged women and even, as is the case, postmenopausal hormone therapy used mainly for CVD prevention has been found to increase the risk of HD.

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Age group	FSH	LH	E1	T4-A	E2
45-49					
Mean	35.45	15.07	42.52	1.39	54.14
StdDev	44.91	16.97	22.89	0.69	39.85
N	239	241	85	93	190
50-54					
Mean	84.29	25.66	29.72	1.28	24.33
StdDev	39.42	13.49	18.72	0.61	28.55
N	207	210	84	86	201
55-59					
Mean	91.58	25.44	27.04	1.26	12.18
StdDev	30.41	10.42	16.14	0.58	7.17
N	156	156	38	38	155
>60					
Mean	80.83	21.32	24.38	1.03	13.27
StdDev	27.30	9.68	10.21	0.42	11.83
N	134	134	40	41	134
Total					
Mean	69.30	21.37	32.85	1.28	27.82
StdDev	44.53	14.35	20.13	0.62	31.99
N					

Table 1. Summary statistics for hormonal markers of reproductive ageing, by age group.

AGE GROUPS						DIFFERENCES BETWEEN AGE GROUPS (ANOVA)	
	45-49	50-54	55-59	>60	total	F	p
Glucose	100.68+13.91 247	103.09+23.84 214	108.38+24.17 157	110.69+34.20 135	104.93+24.23 754	34.692	*
Cholesterol	217.60+38.86 224	229.03+33.89 210	238.69+39.26 153	235.02+36.64 130	228.64+37.96 718	11.836	*
Triglycerides	92.85±41.63 224	94.44±42.39 210	115.27±61.41 153	123.23±77.07 130	103.64±52.0 718	6.901	*
Systolic blood pressure	125.0±17.0 361	130.0±17.0 284	136.0±18.0 173	144.0±21.0 132	131.0±19.0 950	10.935	*
Diastolic blood pressure	80.0±11.0 361	83.0±11.0 283	85.0±12.0 173	87.0±12.0 132	3.0±12.0 950	8.860	*
Weight change	13.17±9.68 376	14.91±9.81 280	15.58±10.73 179	16.47±10.66 133	14.57±10.11 968	6.218	*
Tricipital fat-fold	23.7±6.9 391	25.1±7.0 301	25.0±7.1 196	25.1±14.4 144	24.52±6.93 1032	3.897	*
Subscapular fat-fold	25.2±9.0 391	27.0±0.3 301	26.9±9.6 195	28.3±9.1 143	26.48±9.28 1030	5.812	*
Suprailiac fat-fold	24.1±8.8 392	26.0±9.0 300	27.5±9.6 194	28.7±8.3 143	25.95±9.08 1029	6.218	*
Waist circumference	83.7+9.9 388	86.1±9.4 297	88.4±9.5 192	90.9±9.5 142	86.24±9.93 1019	3.897	*
Hip circumference	102.89.5 388	104.58.2 297	104.5±9.4 192	107.8+9.5 142	104.31±9.23 1019	5.812	*
Waist/hip ratio	0.81±0.06 388	0.82±0.06 297	0.85±0.06 192	0.84±0.07 142	0.83±0.0021 1019	10.882	*
BMI	27.36±4.15 393	28.19±3.95 301	28.573.85 196	29.65±4.09 145	28.15±4.01 1035	6.218	*

Table 2. Mean levels of cardiovascular risk factors and adiposity levels by age group in Spanish women from Alcobendas (Madrid, Spain) aged 45-65 years

	CHOLEST	TRIGLY	GLUC	SBP	DBP	FSH	LHSA	ESTR	ANDRS
TRIGLYC	0.3239***								
GLUCOSE	NS	0.2097**							
SBP	NS	NS	NS						
DBP	NS	NS	NS	0.340***					
FSH	0.2638**	NS	NS	NS	NS				
LH	0.2221**	NS	NS	NS	NS	0.2470***			
ESTRONE	NS	NS	NS	NS	NS	-0.3734***	-0.2710***		
ANDROSTEN.	-0.1643*	NS	NS	NS	NS			0.2258***	
ESTRADIOL	-0.1643*					-0.5768***	0.3807***	0.5959***	0.1757*

Table 3. Partial correlation coefficients (age constant) between cardiovascular risk factors and sex hormones. (N=620. * $p<0.01$, ** $p<0.001$, *** $p\approx0.000$)

	WEIGHT CHANGE	TRICFF	SUBESFF	WAIST C	HIP C	W/H	BMI
CHOLEST	NS	NS	NS	NS	NS	NS	NS
TRIGLYC	0.239***	NS	0.253***	0.324***	0.097*	0.302****	0.208***
GLUCOSE	0.1085*	NS	0.1274**	0.1419**	NS	0.1902	NS
SBP	0.2716***	NS	0.2245***	0.2563***	0.2301***	NS	0.2632***
DBP	0.3044***	0.1040*	0.1984***	0.3031***	0.2632***	NS	0.3010***

Table 4- Partial correlation coefficients (age constant) between cardiovascular risk factors and markers of total fat and fat distribution.

RESULTS OF MULTIPLE LINEAR REGRESION ANALYSIS CARRIED OUT ON EACH OF THE 5 CARDIOVASCULAR RISK FACTOR S CONSIDERED (CVRF)

DEPENDENT VARIABLE: CVRF	AR^2 (%)	COEFFIC.	BETA	SE	T	SIG.
CHOLESTEROL (F=20.22; p=0.000)	9.0	CONSTANT			9.912	0.000
		AGE	0.870	0.359	2.426	0.016
		FSH	0.229	0.043	5.364	0.000
TRIGLYCERIDES (F=24.048; p=0.000)	16.5	CONSTANT			-6.230	0.000
		AGE	2.018	0.541	3.728	0.000
		W/H RATIO	36.362	0.280	7.004	0.000
		WEIGHT CH.	1.860	0.141	3.604	0.000
		SMOKES?	20.947	6.511	3.148	0.002
GLUCOSE (F=10.58; p=0.000)	5.9	CONSTANT			2.290	0.022
		AGE	0.408	0.223	1.831	0.068
		W/H RATIO	50.607	15.298	3.308	0.001
		WEIGHT CH	1909	0.774	2.460	0.014
SYSTOLIC BLOOD PRESSURE (SBP) (F=30.94; p=0.000)	16.7	CONSTANT			5.377	0.000
		AGE	0.110	0.018	6.672	0.000
		WEIGHT CH	0.224	0.080	2.788	0.005
		FSH	-0.0006	0.002	2.861	0.004
		BMI	-0.0006	0.025	2.648	0.008
DIASTOLIC BLOOD PRESSURE (F= 25.180; p= 0.000)	14.5	CONSTANT			7.840	0.000
		AGE	4.072E-2	0.199	3.666	0.000
		WEIGH CH	0.049	0.196	3.803	0.000
		BMI	3.841E-02	0.015	2.507	0.012

B1 PREDICTORS: AGE, MENOPAUSAL STATUS (MENOPAUSE NO/YES),
B2 PREDICTORS: FSH, E2, WAIST/ HIP RATIO (W/H), BODY MASS INDEX, WEIGHT CHANGE, SMOKES?

Table 5. Relative contribution of reproductive ageing, age, adiposity, fat distribution and weight change.

CARDIOVASCULAR RISK FACTORS	N	PREVALENCE
HYPERCHOLESTEROLAEMIA (>=240 mg/dl)	216/617	35.0
HYPERTRIGLYCERIDAEMIA (>=150 mg/dl)	87/617	14.1
HYPERGLYCAEMIA (>= 110 mg/dl)	134/647	20.7
OBESITY (BMI>=30Kg/M^2)	207/849	24.4
WEIGHT INCREASE (>20 Kg)	218/845	25.8
WAIST/HIP RATIO (>0.85)	228/842	27.1
SYSTOLIC HYPERTENSION (SBP>=150 mmHg)	90/836	10.8
DIASTOLIC HYPERTENSION (DBP<=95 mmHg)	104/835	12.5
TOBACCO USE (YES)	140/910	10.8
DIAGNOSED DIABETES	57/900	6.3
TREATMENT FOR HYPERTENSION	132/787	16.8

Table 6- Cardiovascular risk profile of Spanish women living in Alcobendas, Madrid.

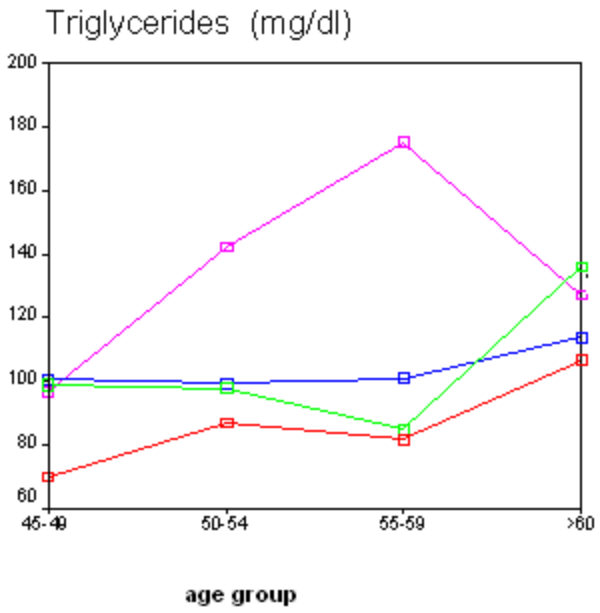

Fig 1- Variation in triglycerides level, according to age and weight change (results of GLM, dependent variable: triglycerides; factors: age, weight change and tobacco use; covariables: waist/hip ratio, cholesterol, factors.

- No weight change or weight loss along reproductive life.
- Weight increase 0-8 kg
- Weight increase 8.1-21 Kg
- Weight increase 21+ Kg

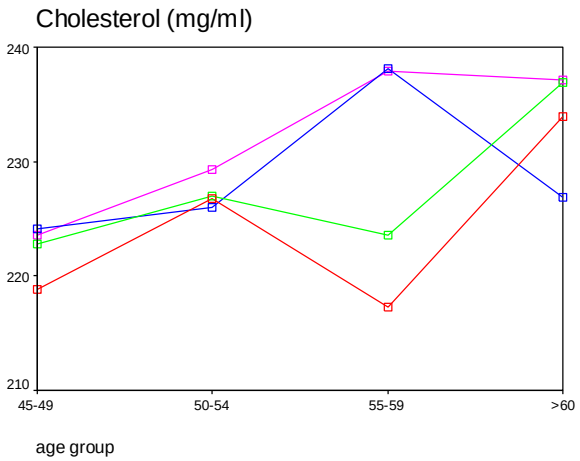

Figure 2- Variation in cholesterol level according to age and weight chang (results of GLM, dependent variable: cholesterol; factors: age and weight change; covariable: FSH).