Cardiovascular Risk Factor Progression in Young Males at 15-Year Follow-Up in the General Military Academy of Zaragoza (AGEMZA) Study

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Introduction and objectives. The AGEMZA cohort comprises military men whose risk factors were studied in 1985 when they were 20 years old. As these men reached the age of 35 years, we investigated the stability of or changes in anthropometric measures, lipid levels and arterial pressure, and looked for interrelationships between any changes.

Methods. In 2000, we collected new data (by cross-sectional study) on body mass index (BMI), cholesterol, cholesterol fractions, triglycerides and blood pressure, which could be compared with the original data. Persistence or tracking was evaluated using standardized regression coefficients and odds for persistence within the same quintile. Current data were modelled using multivariate regression models.

Results. In the 250 subjects studied, significant changes were observed in the following variables: weight +12.1 kg, BMI +3.9 kg/m², cholesterol +68.0 mg/dL, HDL cholesterol –5.2 mg/dL, LDL cholesterol +57.9 mg/dL, and triglycerides +76.3 mg/dL. The degree of persistence was high for all variables, except for diastolic blood pressure. Persistence was most pronounced for BMI, cholesterol, and LDL cholesterol. The changes observed indicate an increase in cardiovascular risk that adds to the effect of aging. The change in lipid profile was mainly influenced by the increase in BMI experienced, whereas blood pressure was mainly influenced by the final BMI attained. In addition, being a current smoker was associated with worse cholesterol fractions and triglyceride levels.

Conclusions. Cardiovascular risk factors increase during the third decade of the life. Early evaluation (after adolescence) enables the identification of individuals who will later be at an increased risk. Modifiable risk factors were identified, such as weight increase and smoking. Preventive measures should be designed for these groups.

Key words: Cohort. Cholesterol. Lipids. Cardiovascular risk factors. Hypertension.

Evolución de los factores de riesgo cardiovascular en jóvenes varones tras 15 años de seguimiento en el estudio Academia General Militar de Zaragoza (AGEMZA)

Introducción y objetivos. La cohorte AGEMZA son varones militares cuyos factores de riesgo fueron estudiados en 1985 a la edad de 20 años. A la edad de 35 años se estudian la antropometría, los lípidos y la presión arterial y se investiga su estabilidad, sus cambios y la interdependencia en su evolución.

Métodos. En 2000, se obtuvieron datos (encuesta transversal) que se compararon con los originales: índice de masa corporal (IMC), colesterol y sus fracciones, triglicéridos y presiones arteriales. La persistencia o tracking se evaluó mediante el coeficiente de regresión estandarizado y la permanencia en quintiles. Se crearon modelos de regresión multivariante para los datos actuales.

Resultados. Tras estudiar a 250 sujetos, se observaron modificaciones significativas de los siguientes facto-
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ABREVIATIONS

AGEMZA: Academia General Militar de Zaragoza (Zaragoza General Military Academy).
BMI: body mass index.
HDL: high density lipoprotein.
LDL: low density lipoprotein.

INTRODUCTION

Although cardiovascular diseases represent the clinical manifestation of advanced atherosclerosis, the atherosclerotic process starts developing during the early stages of life.1 During the first years of adult life, we acquire certain habits and customs that include the type of diet, a sedentary lifestyle and smoking. As later modification of these habits is difficult, they undermine our cardiovascular health during later years.2 It is therefore interesting to determine which cardiovascular risk factors are already present at the end of adolescence, bearing in mind that their tracking will establish, to a great extent, future cardiovascular risk.3–7 The aims of this study were to examine the cardiovascular risk factors and their changes over 15 years in a cohort of young adults, who were all healthy and physically very active at the start of the study. More precisely, as well as determining the persistence of these factors, we wanted to observe and describe the changes produced during this period and to analyze the interdependence of the evolution of the factors studied.

METHODS

The original AGEMZA cohort (corresponding to cadets at the General Military Academy from the intakes of 1985, 1986, and 1987) was studied in small groups (80 subjects) each 3 months, so that the review was completed in three natural years (from 2000 to 2002). The original cohort included 411 persons, but for unforeseen circumstances beyond our control it was not possible to review one of the groups; accordingly, a total of 342 persons from the original cohort were reviewed.

The participants were invited to participate individually by post and at a joint meeting as well. They were all provided with detailed information about the study and gave their written consent to participate. As well as the survey data, other information obtained included analytical and physical examination...
data. The participants were given questionnaires regarding their health habits (nutrition, toxic habits, and physical activity) and a fasting blood sample was obtained at the military installations. Smokers were considered to be those persons who smoked at the time of the survey or those who had smoked during the previous 12 months. The health examination was undertaken at the Cardiovascular Research Unit of the Hospital Clínico Universitario Lozano Blesa in Zaragoza. This examination included anthropometric blood pressure measurements, as well as the following laboratory tests: a 12-lead electrocardiogram, an exercise stress test on a treadmill, a Doppler echocardiogram, and a study of endothelial function by means of the technique of flow-mediated dilation in the humeral artery. The data obtained from these complementary studies will be provided in other reports. Persons involved in this second survey were considered as situation B whereas those involved in the original study were considered to be in situation A. The notation A will be used to designate the difference between these 2 situations.

Trained personnel performed the anthropometric measurements, which were complemented with measurements of impedanciometry whilst standing. The blood pressure was measured with the subject seated after 10 minutes rest, with homologated OMRON electronic devices. The blood samples were processed at the biochemical laboratory of the Hospital Clínico Universitario in Zaragoza. Part of the serum and the plasma obtained were frozen at –70°C for future measurements. This paper presents the results of the lipid parameters. The total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured with a Roche/Hitachi Modular Analytics autoanalyzer (Roche Diagnostics, Indianapolis, IN). Low-density lipoprotein (LDL) cholesterol was calculated from the Friedewald equation,\(^1\) with a maximum limit for triglycerides of 400 mg/dL. All the laboratory measurements were submitted to the usual rigorous quality control protocolized in the laboratory.

The statistical analysis was carried out with the program SPSS 10.0. We used the Student t test for paired samples and Pearson’s correlation coefficient. A linear regression analysis was undertaken.

The tracking was evaluated with the value of the standardized regression coefficient of the original variables to model the final variables and also with the proportion of subjects who remained in the same risk quintile for each variable. We also calculated the odds ratio of remaining in the risk quintile as compared with changing to another quintile.

The variables of the final point (B) were adjusted with multivariate linear models. Possible explanatory variables incorporated to each model included all the original variables (A) except for height and weight (i.e., body mass index [BMI], cholesterol, fractions, triglycerides, heart rate, blood pressure, and smoking status), forcing the initial value of the modeled variable to be present at all times. Moreover, we also included the variable increase in BMI (A), excluding others to avoid colinearity (based on a previous examination of the bivariate correlations, not presented here). The candidate variables were incorporated to the model progressively when they fulfilled the significance criteria.

All the hypothesis tests were calculated bilaterally and a statistical significance threshold was set at .05.

**RESULTS**

We accessed paired longitudinal data for 250 persons in the AGEMZA study; with initial values (15 years previously) and current values (participation rate in the follow-up, 73.1%). Owing to a defect in the initial data, only 143 persons had paired data available for blood pressure and heart rate. No significant differences were found between the increases of the other variables in this subgroup and those who lacked these data, except for the fact that these latter were followed up for 10 months more, a difference in time that we consider insignificant in relation with the whole study period. Persons from the original cohort who were not fully evaluated also had very similar clinical data to those who were reviewed. No participant was taking any cardioactive or lipid lowering drugs at the time of the study.

Table 1 summarizes the study data (anthropometry, blood pressure, lipid profile) of the participants at both points, as well as the changes noted. Table 2 presents the persistence parameters of tracking (standardized

### TABLE 1  Anthropometric, Blood Pressure, and Lipid Profile Changes*

<table>
<thead>
<tr>
<th></th>
<th>No. Mean A</th>
<th>Mean B</th>
<th>Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>250</td>
<td>19.8</td>
<td>35.4</td>
<td>15.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>250</td>
<td>176.9</td>
<td>176.8</td>
<td>0.0</td>
</tr>
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<td>Weight, kg</td>
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<td>69.7</td>
<td>81.8</td>
<td>12.1</td>
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<td>250</td>
<td>22.3</td>
<td>26.1</td>
<td>3.9</td>
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<td>Total chol, mg/dl</td>
<td>250</td>
<td>145.1</td>
<td>213.1</td>
<td>68.0</td>
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<tr>
<td>HDL-C, mg/dl</td>
<td>250</td>
<td>59.9</td>
<td>54.8</td>
<td>–5.2</td>
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<tr>
<td>LDL-C, mg/dl</td>
<td>250</td>
<td>74.5</td>
<td>132.4</td>
<td>57.8</td>
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<tr>
<td>Trig, mg/dl</td>
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<td>53.0</td>
<td>129.3</td>
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<tr>
<td>HR, min⁻¹</td>
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<td>72.2</td>
<td>85.0</td>
<td>–12.7</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>143</td>
<td>126.7</td>
<td>122.5</td>
<td>–4.2</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>143</td>
<td>72.6</td>
<td>74.3</td>
<td>1.8</td>
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</tbody>
</table>

* Indicates initial situation at the start of the study (1985-87); B, final situation at the end of the study (2000-02); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; total chol, total cholesterol; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; trig, triglycerides.
regression coefficient, percentage of those who remained in the risk quintile and the advantages of remaining in the quintile of the study variables.

For the multivariate models, correlation coefficients were used prior to examining the associations between the risk factors at points A and B, the associations of the factors at point B with the increases detected (δ), and the associations of the increases found (δ) with the factors at point A (coefficients that are not reported numerically in this paper).

Briefly, the HDL cholesterol, the triglycerides and the final blood pressure figures (B) covered with less intensity with their initial values (A) than the other variables at the same time as they experienced a greater change with the changes in weight (Δ). The increases (Δ) of each variable mainly had negative correlations with the initial values (A), which may be partly explained by a phenomenon of regression to the mean. All the increases in the lipid parameters covered with the anthropometric variation.

Figure 1 shows an example of the main findings of the study in the evolution of the LDL cholesterol: the parameter was persistently high, all the participants underwent notable worsening and, in the case of differences, these depended partly on the increase of weight.

We found 61 participants who were smokers at the final point (24.4% of the cohort). The rate of smokers was not substantially changed when compared with the years 1985 to 1987 (26.4%), although the smokers smoked more cigarettes per day at the final point. Nevertheless, about 20% of the participants changed their smoking status from smoker to non-smoker. Those participants who ceased smoking had significantly greater increases in BMI and final BMI than the smokers and those who continued smoking. The participants who had smoked at any time, whether or not they were current smokers, had a significantly worse evolution in BMI, cholesterol fractions, and triglycerides. The current smokers also had a trend towards a worse evolution of these parameters, though the differences, these depended partly on the increase of weight.
For the later elaboration of the models, it was decided to try to include the status of “smoker at any time” or “current smoker.”

Modeling of the current variables (B) showed that the models for blood pressure included the original BMI and its increase, which suggested that the final BMI should be included instead. This modification was made for all the variables, but in the case of the cholesterol fractions the models included the original BMI and the final BMI with opposite signs, suggesting a better fit with the increase. A third, more definitive generation of models was tried, which included the original variables, the increase in BMI and the final BMI. In this case, the models included the increase in BMI for the lipid variables and their final value for the blood pressure variables, as can be seen in Table 3. We also added the variables of smoking on to these models of lipids. The variable “smoker at any time” failed to present criteria to form part of the models. However, some models did include the variable “current smoker”; although the variables included were not substantially modified, they did reflect a better fit.

Modeling of the increase experienced (Δ) gave an almost identical result in the variables included, though it presented negative coefficients for the initial values of each variable, which may probably partly represent their regression to the mean. These models are not included within this report as they add no new information.

DISCUSSION

This report provides information about the changes detected in various anthropometric, lipid, and blood pressure variables in a cohort of men of similar age over a period of 15 years, from the time they were young adults until they reached the age of 35 years. The participants all performed the same degree of moderate to intense physical activity at the start of the follow-up period and the voluntary participation level was high, facilitating their localization and follow-up over the period.

Three major groups of factors were analyzed, the weighted measurements, serum lipids and blood pressure. We detected a notable overall increase in weight, a mean increase of about 12 kg. This increase was very similar for all the participants, as the variable showed high tracking indexes. A similar behavior was found with the lipid parameters, with an overall, highly persistent worsening; of note among these was the increase in LDL cholesterol of about 60 mg/dL. Figure 1 shows the homogeneity of the phenomenon, thus ruling out the possibility that the rise was due to just a few persons who had much worse figures than the overall mean. We also saw from both the bivariate and the multivariate analyses that the change in weight...
was an important factor in the worsening of the lipid and blood pressure figures.

The increase in weight that we found was greater than that expected from reference data of the Spanish population. Nonetheless, we can use it as a tool for obtaining generalizable estimations to characterize the risk profile in accordance with consensus agreements for obtaining generalizable estimations to characterize the risk profile in accordance with consensus agreements. The most developed methods use general estimation formulas to obtain regression coefficients using multiple revisions for each subject, independently of the intervals between revisions and partial lack of data in different revisions. Our study is not the best for obtaining generalizable estimations to characterize each variable throughout life with a tracking value, as our study involved 2 ages and a homogeneous period was in line with data available from cross-sectional and longitudinal studies. The findings for the systolic blood pressure are difficult to explain. We postulate that within the context of the initial study, the participants reacted with greater stress to having their blood pressure measured, which was followed by the drawing of a blood sample, a factor that was not present at this final study.

The change in the lipid parameters meant that the participants currently have a much more unfavorable risk profile in accordance with consensus agreements of estimation of risk. This rise that we detected in risk factors on top of the increased risk represented by the passage of the years warrants the implementation of preventive measures as early as that of the age of the participants in this study.

The tracking or persistence of a variable or risk factor is a concept that includes stability and the predictive capacity of future values. The parameters that possess this property may be useful for early screening and much attention should be given to the correction of their pathologic values. A great effort has been made, though not yet concluded, to obtain standard parameters for measurements of tracking. The most developed methods use general estimation formulas to obtain regression coefficients using multiple revisions for each subject, independently of age, the intervals between revisions and partial lack of data in different revisions. Our study is not the best for obtaining generalizable estimations to characterize each variable throughout life with a tracking value, as our study involved 2 ages and a homogeneous period for all the participants. But neither was that our objective. Nonetheless, we can use it as a tool for quantification and can select the standardized coefficient of regression (in a bivariate model) plus 2 non-parametric measurements (percentage of participants who remain in the risk quintile and the advantage ratio associated with continuing in the quintile) from the numerous measurements proposed for its description.

We found that during the period studied, the measurements of weight, total cholesterol and LDL cholesterol showed considerable persistence, followed by the other lipid parameters and the systolic blood pressure. The eminently practical measurement that we have chosen tells us that 1 in 2 persons who have high cholesterol levels at the start of a study will still have high levels at the end of the study unless there is some intervention. Notable, too, was the marked worsening in the lipid profile detected in all the participants. In fact, the threshold for the top initial quintile is well below what, under normal conditions, would be a warning, although it detects persons with pathologic values several years later, which should be taken into account for the preventive evaluation of a young population. Some 50% of persons with LDL cholesterol levels above 100 mg/dL at the age of 20 years will have levels over 160 mg/dL 15 years later. This is not contemplated in some longitudinal studies of cardiovascular risk factors, which use fixed thresholds.

The evaluation of the tracking of lipid values after 15 years in our study showed lower values than those of the Spanish population of children and young persons after 6 years. However, prior to concluding that tracking is less in adults, the different time width should be considered. Studies of tracking in adults usually involve higher ages. Ulmer et al. reported similar tracking coefficients for cholesterol and higher coefficients for BMI and triglycerides, which suggests that the age studied in this report may be a transitional period that has to be considered. Indeed, the study by Wilsgaard et al. showed a lower tracking coefficient for triglycerides between 20 and 24 years of age than for the other ranges, which is similar to that found by us. In this latter study, the tracking of total cholesterol and the BMI was found to be greater and that of HDL cholesterol similar to the values we found. The cohort of the Amsterdam Growth and Health Longitudinal Study also showed similar values to the tracking values for total cholesterol and HDL cholesterol. However, our data do not allow us to draw conclusions about the independent tracking of time, and the coefficients obtained by linear regression are usually less than those from groups of data with multiple measurements in the same person.

Our study was not specifically designed to evaluate stability, but rather to analyze the coevolution of the factors, highlighting the importance of the information on weight. The transverse association between...
The multivariate analysis that we carried out for the present study suggests that the lipid values are conditioned by the increase in weight over the age range considered, whereas for the blood pressure figures the degree of overweight appears to be more important. Our model explained 65% of the variability in LDL cholesterol according to the initial values and the change in BMI.

This different behavior in the dependence of the weight values of the blood pressure and the lipids suggests that the pathophysiological mechanisms involved may be different. Indeed, the epidemiological analysis of the associations between the BMI, blood pressure, and dyslipidemia in the Framingham cohort appears to separate these last 2 variables into 2 statistically different factors. For the lipids, it is possible to postulate that the BMI at the age of 20 years represents an adipose or osteomuscular constitution, and that the excess weight later acquired is the cause of the dyslipidemia, i.e., a person who is slim at the start worsens more if they reach the same weight as someone who already had a higher BMI at the start. An explanation for the behavior of the blood pressure is more complex; however, it could be associated with a different demand for irrigation depending on the size of the adipose tissue and would therefore depend on the final status rather than on the increase.

The AGEMZA study has already produced results concerning smoking, which it associated with an increase in the number of peripheral blood leukocytes. The present report shows its influence on the lipid profile, both for the cholesterol fractions and for the triglycerides. Although the association with lower concentrations of HDL cholesterol has been reported in previous studies, the association between smoking and LDL cholesterol or triglycerides is more controversial. In our multivariate models we found that smoking at the final time point of the survey (B) was what remained in the model, though we are unable to rule out that it may perhaps be due to an association of the habit of smoking with a more sedentary lifestyle.

Our study is singular because its objective differed from that of tracking studies, which aim to obtain a generalizable value of persistence at any age. On the other hand, the study provides new data for a Spanish population about an age of weight and lipid changes, with the advantage of simultaneous measurements (at the age of the participants) for the whole cohort, which accounts for the different models for lipids and for blood pressure.

In conclusion, 15 years after the initial analysis, the study sample increased its weight and its BMI by 12.1 kg and 3.9 kg/m², respectively. Likewise, a worsening was seen in the lipid profile, with an increase in total cholesterol, LDL cholesterol and triglycerides, and a reduction in HDL cholesterol, which doubtless imply a worse general cardiovascular risk status, independently of the change in age. A notable persistence was found in the weight and lipid parameters that should enable preventive efforts in similar populations depending on the initial evaluation, always bearing in mind that the thresholds must be different from those of the general population. We saw that the multivariate models which describe the lipids included the increase in BMI and the models that describe the blood pressure included the final BMI, which suggests the existence of different pathophysiological links. In the case of the lipids, smoking was also a negative factor. Thus, the main preventive measure to be applied to young persons like those in our study should be oriented towards the prevention of weight gain and encouraging the cessation of smoking.

REFERENCES

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Rev Esp Cardiol. 2006;59(7):671-8


