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Inequalities in the Distribution of Cardiovascular Disease Risk Factors in Argentina. A Study from the 2005, 2009 and 2013 National Risk Factor Survey (NRFS)

Desigualdades en la distribución de factores de riesgo en enfermedades cardiovasculares en la Argentina. Un estudio a partir de la Encuesta Nacional de Factores de Riesgo (ENFR) de 2005, 2009 y 2013

ABSTRACT

Background: Cardiovascular health inequalities have been documented in the literature in both developed and undeveloped countries and there is an inverse association between the incidence and mortality for specific cause of cardiovascular disease and levels of income, education and employment.

Objective: The aim of this study was to identify the existence of inequalities in the prevalence of risk factors by socioeconomic status in Argentina.

Methods: Data from the 2005, 2009 and 2013 National Risk Factor Surveys (NRFS) were analyzed. The prevalence of obesity, smoking, hypertension and cholesterol were studied. Differences for each risk factor were estimated in relation to socioeconomic status (measured by education, income and health coverage). The independent association between socioeconomic status and risk factors was assessed using logistic regression models.

Results: Educational level was inversely associated with the prevalence of obesity (p<0.01), hypercholesterolemia (p<0.01), hypertension (p<0.01) and smoking (p<0.05) and the effect varied by gender and age group. Income level was significantly and inversely associated with the prevalence of hypertension (p<0.01). The temporal evolution of inequalities indicates there was no attenuation between surveys and, on the contrary, it showed an increase in smoking gaps.

Conclusions: Deep inequalities were recorded in the distribution of cardiovascular risk factors by educational level. Groups with high burden of risk factors are vulnerable populations upon which preventive policies should be targeted.

Key words: Risk Factors - Obesity - Hypertension - Smoking - Hypercholesterolemia – Inequalities

RESUMEN

Introducción: Las desigualdades en salud cardiovascular se han documentado en la literatura tanto en países desarrollados como no desarrollados y existe una asociación inversa entre la incidencia y mortalidad por causa específica de enfermedades cardiovasculares y los niveles de ingreso, educación y empleo.

Objetivo: Identificar la existencia de desigualdades en la prevalencia de factores de riesgo por nivel socioeconómico en la Argentina.

Material y métodos: Análisis de los datos de la Encuesta Nacional de Factores de Riesgo (ENFR) de 2005, 2009 y 2013. Se estudió la prevalencia de obesidad, tabaquismo, hipertensión arterial y colesterol. Se estimaron las brechas para cada factor de riesgo en relación con el nivel socioeconómico (medido con educación, ingreso y cobertura de salud). La asociación independiente entre nivel socioeconómico y factores de riesgo se evaluó con modelos de regresión logística.

Resultados: El nivel educativo se asoció inversamente con la prevalencia de obesidad (p < 0,01), hipercolesterolemia (p < 0,01), hipertensión arterial (p < 0,01) y tabaquismo (p < 0,05) y el efecto varió por grupos de edad y sexo. El nivel de ingreso se asoció significativamente y de manera inversa con la prevalencia de hipertensión (p < 0,01). La evolución temporal de las desigualdades indica que no hubo atenuación de estas entre las encuestas y, por el contrario, muestra un incremento en las brechas de tabaquismo.

Conclusiones: Se registraron profundas desigualdades en la distribución de factores de riesgo cardiovascular por niveles educativos. Los grupos con elevada carga de factores de riesgo constituyen poblaciones vulnerables sobre las cuales deberían orientarse políticas preventivas.

Palabras clave: Factores de riesgo - Obesidad - Hipertensión - Tabaquismo - Hipercolesterolemia – Desigualdades

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INTRODUCTION

Health inequalities by socioeconomic status have been well documented in the literature both in developed and undeveloped countries. The Black report presentation in 1980 showed that health inequalities linked to socioeconomic status had increased despite the introduction of the British National Health System 40 years ago. (1) The health of the poor had improved; however, that of the rich had improved much more. More recent studies continue to reveal obvious gaps in health gradients both among countries and within them, and the reduction of these inequities (unfair and avoidable inequalities) remain a challenge for public health.

Studies show the inverse relationship between morbidity and mortality and social class. Socioeconomic status indicators commonly used in the literature have been education, occupation and income, and these results are maintained, regardless of the indicator used to measure them. (2-4) The same inverse relationship was documented between socioeconomic status and cardiovascular morbidity and mortality as well as its major risk factors (obesity, smoking, hypertension and high cholesterol). (5-11)

Because cardiovascular diseases are preventable and the adoption of strategies based on the control of risk factors (RF) to avoid them is an effective means to guide health policies, proper knowledge of the most vulnerable social situations could guide these policies to improve the population overall health outcomes.

The aim of our study was to analyze the pattern of cardiovascular RF in relation to social class using the 2005, 2009 and 2013 National Risk Factor Survey (NRFS), measuring education, income level and health insurance coverage inequalities.

METHODS

Data and variable definition

An analysis of secondary data from the 2005, 2009 and 2013 NRFS was performed. The NRFS is part of the Non-communicable Disease (NCD) Surveillance System and of the Integrated System of Household Surveys (ISHS) which is performed every 4 years following an agreement among the National Ministry of Health, the National Institute of Statistics and Censuses and the Statistics Provincial Directorates.

The survey covers the population aged 18 years or older who live in private households in towns of 5,000 or more inhabitants of Argentina. The effective response rate for the third edition was 70.7%, including 32,365 people in the analysis. Previous editions had effective response rates of 86% (2005) and 79% (2009). (12) Surveys provide information on housing conditions and socioeconomic aspects of head of household (gender, age, marital status, education, income, employment status, type of health coverage) and individual information corresponding to general health, prevalence of NCD and prevalence of cardiovascular RF (overweight and obesity, high blood pressure, cholesterol and smoking).

Household income level (cutoff values in three categories: low, medium and high according to similar purchasing power for each year), education level and explicit health coverage were used as measures of socioeconomic status.

Analyses were performed for the whole sample and by gender and age groups, divided in the following age ranges: 18-34, 35-49 and 50 or more years.

Definition of risk factor

Body Mass Index (BMI), calculated as weight in kilograms divided by height in square meters, defined normal weight as BMI<25, overweight as BMI≥25 and <30 and obesity as BMI≥30, according to World Health Organization (WHO) recommendations.

Hypertension and hypercholesterolemia were estimated as the ratio between those who had the report of a health professional and those who reported having measured their risk factor in the last 2 years.

An individual who currently smokes cigarettes everyday or some days and who throughout his life had smoked at least 100 cigarettes was considered a smoker.

Statistical analysis

Qualitative variables were described using totals, percentages and 95% confidence intervals (95% CI) and continuous data were expressed as means and 95% CI; both estimations were performed using weightings arising from the complex sampling design.

The association between socioeconomic status categories and prevalence of RF was assessed with the chi-square test for linear trends. Also, the absolute differences between the most favored and most disadvantaged groups were quantified. To evaluate the association between cardiovascular RF and social status in the different age and gender strata, the prevalence ratios between the extreme categories of socioeconomic indicators were calculated.

Multivariate logistic regression models were built with each RF as dependent variable to assess the gaps in the prevalence of each RF by income, education and health coverage level, controlling for confounders. In addition to socioeconomic indicators, gender, age group, region of residence and year of survey were included as independent variables. Furthermore, interactions between variables of interest and year of survey were incorporated in order to identify changes in gap evolution. These models incorporated weighting, stratification and sampling stages. Odds ratios (OR), their 95% CI and the corresponding p values were reported.

A p value <0.05 was considered statistically significant.

All analyzes were performed using Stata version 13 statistical package (StataCorp LP, College Station, TX, USA)

Ethical considerations

The NRFS is part of the epidemiological surveillance strategies and Law 17.622 of Statistical Secrecy, and was also incorporated as survey to the INDEC National Statistical
System. The law guarantees the anonymity of respondents and confidentiality of information in processing phase. In addition, each participant was asked to orally express his participation consent. In order to comply with the Declaration of Helsinki requirements, the NRFS was approved by the Ethics Committee of the Pan American Health Organization.

RESULTS

Table 1 shows sociodemographic characteristics of the individuals who answered the survey and presented valid data for analysis. In 2013, 31% reported having complete primary school, 41% complete secondary school and 27% incomplete or complete higher education (tertiary or university). The relative frequency of income categories in 2013 was 39% low income, 45% middle income and 15% high income. Health coverage increased from 60% to 69% between 2005 and 2013.

Obesity recorded a significant increase from 16% in 2005 to 21% in 2013. The 30-54 year-old group had the highest growth (7% absolute increase between 2005 and 2013). On the other hand, the increase was more pronounced in men (from 15% to 23%) than in women (14% to 19%). The prevalence of both hypertension and elevated cholesterol showed no significant changes in the period. Conversely, smoking was significantly reduced from 30% to 25%.

Tables 2 and 3 detail the RF prevalence, absolute difference and prevalence ratio between extreme categories, by education and income level, respectively, for 2013. Obesity showed significant inequalities according to socioeconomic groups, mainly associated to education level. Its prevalence was 28% among individuals who reported primary education compared to 14% among those who reported higher education levels. Inequality was higher among women than in men, due to the lower prevalence of obesity in women with higher education levels. When analyzed by age group, the prevalence increased and inequality was maximum for the middle age group (30-55 years). Inequalities decreased when the level of income was used as an indicator of socioeconomic status; however, they

| Table 1. Sociodemographic characteristics and risk factors of the study population. |
|-----------------------------------------------|---------------|---------------|---------------|
| Age average (years)                          | 43.3 (42.9-43.7) | 43.6 (43.1-44.1) | 43.3 (42.6-44.1) |
| Men, %                                        | 47.5 (46.4-48.7) | 46.7 (46.1-47.3) | 47.4 (46.5-48.4) |
| Working status, %                             |                |                |                |
| Employed                                      | 62.8 (61.7-63.9) | 62.9 (61.9-63.9) | 62.7 (61.3-64.1) |
| Unemployed                                    | 5.5 (5.0-6.0)   | 5.2 (4.3-6.2)   | 4.35 (3.7-5.0)  |
| Inactive                                      | 31.7 (30.7-32.7) | 31.9 (30.6-33.1) | 33.0 (31.8-34.1) |
| Income level, %                               |                |                |                |
| Low income                                    | 43.5 (42.0-45.0) | 42.2 (38.6-45.7) | 39.0 (35.4-42.6) |
| Middle income                                 | 39.7 (38.4-41.0) | 42.4 (40.8-44.0) | 45.5 (44.3-46.8) |
| High income                                   | 16.8 (15.8-17.9) | 15.5 (13.1-17.8) | 15.5 (12.5-18.5) |
| Education level, %                            |                |                |                |
| Complete primary education                    | 39.1 (37.8-40.4) | 33.5 (29.6-37.3) | 31.4 (27.1-35.8) |
| Complete second. education                    | 36.9 (35.8-38.0) | 39.7 (37.5-42.0) | 41.2 (39.6-42.9) |
| Higher education                              | 24.0 (22.7-25.2) | 26.8 (21.4-32.3) | 27.3 (21.7-33.0) |
| Explicit health coverage, %                  |                |                |                |
| With coverage                                 | 60.9 (59.4-62.3) | 67.8 (63.6-72.0) | 69.5 (64.6-74.4) |
| Cardiovascular risk factors                   |                |                |                |
| Body mass index, %                            |                |                |                |
| Normal weight                                 | 50.9 (49.8-52.1) | 46.5 (44.6-48.4) | 42.1 (39.7-44.6) |
| Overweight                                    | 34.4 (33.4-35.5) | 3545 (34.7-36.2) | 37.1 (35.6-38.5) |
| Obesity                                       | 14.6 (13.9-15.4) | 18.0 (16.6-19.4) | 20.8 (19.6-22.1) |
| Hypertension, %                               | 34.5 (33.4-35.6) | 34.6 (32.8-36.3) | 34.1 (32.7-35.5) |
| Hypercholesterolemia, %                       | 27.8 (26.5-29.1) | 29.1 (28.1-30.2) | 29.8 (28.6-31.0) |
| High blood sugar/diabetes, %                  | 8.4 (7.8-9.1)   | 9.6 (9.1-10.1)   | 9.8 (9.3-10.0)   |
| Smoking, %                                    | 29.7 (28.7-30.8) | 27.1 (25.9-28.3) | 25.1 (24.2-26.1) |
| Total observations                            | 41.392 | 34.732 | 32.365 |
remained in the middle age group. (Table 3)

Gaps in the prevalence of hypertension by education level are very significant; the lowest level group doubles that of the highest level (48% vs. 23%). In addition, the prevalence in women in the lower education level was significantly higher than in men (53% vs. 43%). These gender differences were not observed in the remaining education levels. Regarding inequalities by age group most occurred in those under 30 years where, although the prevalence was lower, there was almost a 4-fold difference between primary vs. higher education level. Gaps by income level were statistically significant for all groups.

Relative hypercholesterolemia inequalities reached 37% between the highest and lowest education levels, and in absolute terms the gap was 10%. Both absolute and relative gaps were higher in women than in men, concentrated in the middle age group. The analysis results by income level were less robust, only showing statistically significant differences in women.

Smoking prevalence for the primary level of education was 26% vs. 21% for the higher education level, reaching 31% in men with primary education and 32% for the group <30 years with the same education level. Table 4 shows the results of the multivariate models for each RF and for the presence of at least three

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**Table 2. Risk factor prevalence, absolute difference and prevalence ratio among education levels by age groups and gender in 2013.**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Age group</th>
<th>Gender</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;30 years</td>
<td>30 - 54 years</td>
<td>&gt;55 years</td>
</tr>
<tr>
<td></td>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
<td>Prevalence (%)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete primary ed.</td>
<td>14 (11.8-16.8)</td>
<td>30 (27.4-32.4)</td>
<td>30 (27.6-31.5)</td>
</tr>
<tr>
<td>Complete second ed.</td>
<td>11 (9.8-12.8)</td>
<td>25 (23.0-26.9)</td>
<td>25 (21.8-27.7)</td>
</tr>
<tr>
<td>Tertiary and u.</td>
<td>5 (30-7.4)</td>
<td>17 (15.4-18.9)</td>
<td>23 (17.3-27.8)</td>
</tr>
<tr>
<td>Absolute difference</td>
<td>9%</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Prevalence ratio</td>
<td>2.77</td>
<td>1.75</td>
<td>1.31</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete primary ed.</td>
<td>28 (24.4-32.2)</td>
<td>36 (33.1-38.5)</td>
<td>62 (59.9-64.6)</td>
</tr>
<tr>
<td>Complete second ed.</td>
<td>17 (15.2-19.7)</td>
<td>29 (26.5-31.1)</td>
<td>56 (52.3-59.8)</td>
</tr>
<tr>
<td>Tertiary and u.</td>
<td>8 (6.0-9.5)</td>
<td>22 (18.7-26.2)</td>
<td>50 (45.6-54.4)</td>
</tr>
<tr>
<td>Absolute difference</td>
<td>21%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Prevalence ratio</td>
<td>3.65</td>
<td>1.59</td>
<td>1.24</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete primary ed.</td>
<td>13 (8.3-17.3)</td>
<td>35 (31.9-37.3)</td>
<td>39 (36.4-41.8)</td>
</tr>
<tr>
<td>Complete second ed.</td>
<td>16 (12.7-19.0)</td>
<td>26 (23.9-28.2)</td>
<td>38 (34.6-41.8)</td>
</tr>
<tr>
<td>Tertiary and u.</td>
<td>16 (12.2-19.3)</td>
<td>25 (23.1-27.6)</td>
<td>41 (36.9-44.3)</td>
</tr>
<tr>
<td>Absolute difference</td>
<td>3%</td>
<td>9%</td>
<td>-1%</td>
</tr>
<tr>
<td>Prevalence ratio</td>
<td>0.81</td>
<td>1.37</td>
<td>0.96</td>
</tr>
<tr>
<td>p value</td>
<td>&gt;0.10</td>
<td>&lt;0.01</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete primary ed.</td>
<td>42 (37.3-47.2)</td>
<td>32 (29.1-34.0)</td>
<td>16 (14.7-17.8)</td>
</tr>
<tr>
<td>Complete second ed.</td>
<td>32 (29.3-33.8)</td>
<td>28 (26.0-29.7)</td>
<td>18 (14.9-20.2)</td>
</tr>
<tr>
<td>Tertiary and u.</td>
<td>20 (16.7-22.3)</td>
<td>23 (21.1-24.8)</td>
<td>17 (13.8-20.1)</td>
</tr>
<tr>
<td>Absolute difference</td>
<td>23%</td>
<td>9%</td>
<td>-1%</td>
</tr>
<tr>
<td>Prevalence ratio</td>
<td>2.16</td>
<td>1.37</td>
<td>0.96</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&gt;0.10</td>
</tr>
</tbody>
</table>
of them (last column). After adjusting for potential confounders, education level was inversely associated with all RF except smoking. Income level was only inversely associated with hypertension. In addition, there were no changes in inequalities over time, as evidenced by the lack of significance in terms of interaction between year and income and education level, except for smoking, where increases in inequalities were observed between successive surveys.

**DISCUSSION**

The results of this study show statistically significant associations between social class inequalities measured by education level, income and health coverage and its relationship with the prevalence of cardiovascular RF in the Argentine population over 18 years of age. These inequalities in the analyzed RF are present since early stages of life (18-30 years) and their intensity is more strongly associated with education level.

Data of the present analysis are consistent with other studies that show an increased prevalence of cardiovascular RF with age. (13, 14) Furthermore, our results indicate that differences by education level decrease with age for hypertension, hypercholesterolemia and smoking while an inverted U-shaped effect is observed for obesity, with a maximum gap for

### Table 3. Risk factor prevalence, absolute difference and prevalence ratio among income levels by age group and gender in 2013.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>13-24.4</th>
<th>25-34.3</th>
<th>35-44.3</th>
<th>45-54.3</th>
<th>55-64.3</th>
<th>65-74.3</th>
<th>75-84.3</th>
<th>85-94.3</th>
<th>95-104.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>26.9-32.8</td>
<td>30.6-34.2</td>
<td>33.4-37.1</td>
<td>36.2-40.0</td>
<td>39.0-42.8</td>
<td>41.8-45.7</td>
<td>44.6-49.5</td>
<td>47.4-52.3</td>
<td>50.2-55.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39.5-43.2</td>
<td>42.2-46.0</td>
<td>44.9-48.7</td>
<td>47.6-51.4</td>
<td>50.3-54.1</td>
<td>53.0-56.8</td>
<td>55.7-60.5</td>
<td>58.4-62.2</td>
<td>60.1-64.0</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>32.0-35.8</td>
<td>34.7-38.5</td>
<td>37.4-41.2</td>
<td>39.1-43.0</td>
<td>40.8-44.6</td>
<td>42.5-46.3</td>
<td>44.2-48.0</td>
<td>45.9-50.0</td>
<td>47.6-51.4</td>
</tr>
<tr>
<td>Smoking</td>
<td>24.0-27.8</td>
<td>26.7-31.5</td>
<td>29.4-34.2</td>
<td>32.1-37.0</td>
<td>34.8-41.0</td>
<td>37.5-44.5</td>
<td>40.2-50.0</td>
<td>42.9-49.5</td>
<td>45.6-52.1</td>
</tr>
</tbody>
</table>

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the age group between 30 and 55 years. The intensity of inequality appears to be higher in women than in men in the case of high blood pressure, and lower for obesity and smoking.

Regarding the evolution of inequalities, not only did they not decrease, but in the case of smoking it increased significantly. These results are discouraging and highlight the need to address swift measures in this regard, such as pricing policies which could alter relative prices, increasing access barriers for tobacco

**Table 4. Multivariate analysis of cardiovascular risk factor determinants (2005, 2009 and 2013 NRFS).**

<table>
<thead>
<tr>
<th></th>
<th>BMI&gt;30</th>
<th>Hypertension</th>
<th>Hypercholesterolemia</th>
<th>Smoking</th>
<th>Three or more risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L30-54 years</td>
<td>2.47***</td>
<td>1.74***</td>
<td>1.93***</td>
<td>1.00</td>
<td>2.63***</td>
</tr>
<tr>
<td>≥54 years</td>
<td>2.81***</td>
<td>4.93***</td>
<td>4.16***</td>
<td>0.41***</td>
<td>3.51***</td>
</tr>
<tr>
<td>Men=1</td>
<td>1.10**</td>
<td>0.64***</td>
<td>0.90</td>
<td>1.78***</td>
<td>1.21</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete second. education</td>
<td>0.90**</td>
<td>0.89***</td>
<td>0.94</td>
<td>1.16***</td>
<td>1.11</td>
</tr>
<tr>
<td>Higher: Tertiary and university</td>
<td>0.66***</td>
<td>0.62***</td>
<td>0.77***</td>
<td>0.95</td>
<td>0.64***</td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle income</td>
<td>1.11</td>
<td>0.87***</td>
<td>1.08*</td>
<td>1.00</td>
<td>1.08</td>
</tr>
<tr>
<td>High income</td>
<td>1.25</td>
<td>0.77***</td>
<td>1.04</td>
<td>1.13*</td>
<td>1.09</td>
</tr>
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*** p<0.01; ** p<0.05; * p<0.10
NRFS: National Risk Factor Survey. BMI: Body mass index. OR: Odds ratio
smoking in the most vulnerable groups.

A further aspect, particularly evident in the case of hypertension is that different socioeconomic indicators provide independent and complementary information on inequities, emphasizing the importance of measuring more than one indicator in epidemiological studies. (15).

The results presented should be interpreted in the context of the limitations inherent to the design. Because this is an observational study, the associations reported could be due to unmeasured confounders; however, this inverse association between socioeconomic status and RF has been reported in other studies. (16, 17) Non-response (14% for the 2005 NRFS and 30% for 2013 NRFS) could induce selection bias. In addition, difficulties in measuring income, including the absence of continuous metrics, could have resulted in less robust associations between this socioeconomic indicator and RF distribution.

CONCLUSIONS

The reduction of the inequalities observed in cardiovascular risk should be a priority in public policies in general and particularly in health policies, with the aim of reducing the burden of associated morbidity and mortality. A clear focus should be established in controlling the rapid growth of obesity and the decrease in the prevalence of certain RF (mostly smoking), but also in extending strategies towards the reduction of the socioeconomic status gaps observed in this study, as a crucial factor of access to a better health care and condition.

Conflicts of interest

None declared

(See authors’ conflicts of interest forms in the web/Supplementary material)

REFERENCES


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