Why should population attributable fractions be periodically recalculated?☆
An example from cardiovascular risk estimation in southern Europe

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A B S T R A C T
Objective. To determine the effect of age and study period on coronary heart disease (CHD) risk attributable to cardiovascular risk factors.

Methods. A cohort of cardiovascular disease (CVD)-free randomly participants from Girona (Spain) aged 35–74 years recruited in 1995 and 2000 and followed for an average of 6.9 years. A survey conducted in the same area in 2005 was also used for the analysis. Smoking, hypertension, diabetes, sedentary lifestyle, obesity, total cholesterol ≥240 mg/dl, low-density lipoprotein (LDL) cholesterol ≥160 mg/dl, and high-density lipoprotein cholesterol <40 mg/dl were the risk factors considered. The composite end-point included myocardial infarction, angina pectoris, and CHD death.

Results. LDL cholesterol had the highest potential for CHD prevention between 35 and 74 years [42% (95% Confidence Interval: 23,58)]. The age-stratified analysis showed that the population attributable risk (PAF) for smoking was 64% (30,80) in subjects <55 years; for those ≥55 years, the PAF for hypertension was 34% (1,61). The decrease observed between 1995 and 2005 in the population’s mean LDL cholesterol level reduced that PAF in all age groups.

Conclusion. Overall, LDL cholesterol levels had the highest potential for CHD prevention. Periodic PAF recalculation in different age groups may be required to adequately monitor population trends.

Introduction
Public health decisions about resource allocation, prevention, and patient care are closely tied to the availability of information on prevalence, incidence, mortality, and case-fatality to address the illnesses with the greatest impact on the population and their determinant risk factors. A key example is our need to understand cardiovascular diseases (CVD), the main cause of death in the developed world, and the associated risk factors (World Health Statistics, 2009).

The population attributable fraction (PAF), the proportion of disease incidence in the population that can be attributed to a risk factor, combines the concepts of incidence (alternatively, relative risk or hazard ratio) and risk factor prevalence (Walter, 1976). The assumptions underlying valid PAF estimation include a causal relationship between risk factors and disease; immediate risk reduction among the exposed, equal to non-exposure, when the risk factor is eliminated from a population; and independence of the considered risk factors from other factors that influence disease occurrence (Northridge, 1995; Rockhill et al., 1998).

PAF magnitude varies with age and region, known to modify risk factor prevalence (Gabriel et al., 2008; Evans et al., 2001; Howard et al., 2009; Yusuf et al. 2004; Menotti et al., 2000). Moreover, secular changes in the prevalence of risk factors also affect PAF values (Evans et al., 2001; Grau et al., 2007). For some risk factors, relative risks or
hazard ratios vary by length of follow-up (Menotti et al., 2005; Menotti and Lanti, 2003), which may slightly influence PAF estimates.

Estimates of relative risk and risk factor prevalence are typically obtained from published data on different populations, regions and time periods (Medrano et al., 2007). Accurate PAF estimation requires relative risk and risk factor prevalence data from the same population.

This analysis aimed to determine the effect of age and study period on 10-year coronary heart disease (CHD) risk attributable to cardiovascular risk factors in a population-based study (CHD-PAF).

Methods

Design

In northeast Spain, a cohort of participants ages 35–74 was randomly recruited from the Girona census in two surveys (1995 and 2000) used to determine 10-year hazard ratios and CHD-PAF for different risk factors by age groups.

Baseline examinations at recruitment and a 2005 survey in the same region permitted analysis of CHD-PAF modifications over 10 years. Participation in all three surveys was 72%. Inclusion criteria and recruitment methodology are previously described (Grau et al., 2007). Only participants free of CVD at baseline were included in analyses. Patients with heart failure of non-CHD origin during follow-up were excluded. Surveys and methods were approved by the local ethics committee; participants were duly informed, provided signed consent, and received their examination results.

Risk factor measurement

A team of trained nurses and interviewers used the same standard questionnaires and measurement methods in all three surveys. Standardized anthropometric measurements determined waist circumference, height and weight. Body mass index (BMI) was calculated as weight (kg) divided by height (cm) squared. Cigarette smoking (current/ex/never) was determined using an administered questionnaire, blood pressure from the average of 2 readings taken at least 5 min apart (Grau et al., 2007), and leisure activities during the previous year by the Minnesota leisure-time physical activity questionnaire, validated for Spain (Elosua et al., 2000, 1994).

Blood was withdrawn within 60 s, after 10–14 h fasting. Serum sample aliquots were stored at −80 °C. Total cholesterol and triglyceride concentrations were determined enzymatically (Roche Diagnostics, Basel, Switzerland). High-density lipoprotein (HDL) cholesterol was measured soluble HDL-cholesterol using an accelerator selective detergent method (ABX-Horiba Diagnostics, Montpellier, France). Analyses were performed by Cobas Mira Plus autoanalyzer using an accelerator selective detergent method (ABX-Horiba Diagnostics, Montpellier, France). Interassay coefficients of variation were 2.5%, 3.2%, 4.5% and 3.8% for total cholesterol, triglycerides and HDL cholesterol.

Exposure criteria

Current smoking was defined as active smoking within the preceding year. Hypertension was defined as use of antihypertensive agents or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 (Chobanian et al., 2003). Diabetes was defined as use of insulin or hypoglycemic agents or fasting blood glucose ≥125 mg/dl. Lifestyle was considered sedentary when average weekly energy expenditure in moderate- to high-intensity physical activity was <1000 kcal. Obesity markers were BMI ≥30 kg/m² for both sexes or waist circumference ≥102 cm for men and ≥88 cm for women. Waist circumference was only measured in a subsample of the 2005 survey. Cut-points for abnormal lipid levels were total cholesterol ≥240 mg/dl, LDL ≥160 mg/dl, and HDL <40 mg/dl (National Cholesterol Education Program III (NCEP III), Expert Panel National Cholesterol Education Program, 2001).

Case ascertainment

Non-fatal events during follow-up were ascertained by telephone questionnaire and medical records review. Fatal events were identified from regional and national mortality registers. The primary composite endpoint event was acute myocardial infarction, angina pectoris, or death from CHD. The secondary composite endpoint further included fatal and non-fatal stroke, and peripheral artery disease. Deaths and suspected CVD events were adjudicated by 2 physicians using established criteria.

Statistical analysis

Analyses of the whole sample and age strata (35–54, 55–74 years) used R Statistical Package (R Foundation for Statistical Computing, Vienna, Austria, Version 2.0). Age was summarized as mean and standard deviation, and categorical variables as proportions.

Cox proportional hazards models were fitted to estimate crude and adjusted CHD risk, with 2 models for each for cardiovascular risk factor: a crude model and one adjusted for age, sex and risk factors that differed between event and non-event participants.

PAFs were estimated for each factor, as follows (Rockhill et al., 1998):

\[
PAF = 1 - \sum P(D|\bar{E}, C) / P(D)
\]

where:

\[
P(D) = \text{Average probability of disease (D) in the population (both exposed and unexposed individuals)},
\]

\[
P(D|\bar{E}, C) = \text{Marginal conditional probability of disease (D) given no exposure (\bar{E}), averaged over strata of potential confounders (C)}.
\]

The Bootstrap method was used to estimate confidence intervals for these PAF point estimates.

A secondary analysis used the same models to estimate the hazard ratios and PAF of CVD events.

To ensure comparability, since 2005 study follow-up has not started, we applied Levin’s formula, which does not require incidence rates and uses unadjusted HR, to estimate non-adjusted PAF for all 3 surveys (Rockhill et al., 1998):

\[
PAF = \frac{|HR − 1| \times Pr}{1 + (HR − 1) \times Pr}
\]

where,

\[
HR = \text{Unadjusted hazard ratio obtained with the cohort follow-up},
\]

\[
Pr = \text{Cardiovascular risk factor prevalence in general population}.
\]

The 1995, 2000, and 2005 prevalence estimates of cardiovascular risk factors (Table 1) used in our PAF estimations are previously published (Grau et al., 2007; Masià et al., 1998).

Results

We followed 1802 men and 1932 women for 25,744 person-years, with 6.9 years mean follow-up. During follow-up, 220 participants (4.7%) were lost, 106 participants suffered an incident CHD event, and 136 died of other causes (Fig. 1). The acute myocardial infarction age-standardized incidence rate was 295 and 94/100,000 men and women, respectively.

The prevalence of baseline hypertension, diabetes, and obesity (per BMI or waist circumference) increased with age, but older participants had lower smoking prevalence at baseline (Table 1). Participants ages 35–54 with a CHD event during follow-up had significantly higher hypertension, diabetes and smoking prevalence.
and higher total and LDL cholesterol levels. Those >54 years with a CHD event were significantly older, more often hypertensive, and presented higher total and LDL cholesterol levels and lower HDL cholesterol. All participants (35–74 years) with a CHD event were significantly older, more often hypertensive, diabetic and smokers, and had higher total and LDL cholesterol levels and lower HDL cholesterol (Table 2).

Age, male sex, total and LDL cholesterol, hypertension, diabetes and smoking were significant predictors of CHD events in people ages 35–54. However, hypertension was no longer significant after adjustment for potential confounders. CHD hazard ratios for age, female sex, total, LDL and HDL cholesterol and hypertension were significantly different from 1 in all adjusted models for people ages 55–74 (Table 3).

Table 1
Cardiovascular risk factors at recruitment in 1995, 2000 and 2005 and number of events during follow-up in the population of Girona, Spain.

<table>
<thead>
<tr>
<th></th>
<th>35–54 years</th>
<th>55–74 years</th>
<th>35–74 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1995</td>
<td>2000</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>n=679</td>
<td>n=1250</td>
<td>n=2908</td>
</tr>
<tr>
<td></td>
<td>n=695</td>
<td>n=1110</td>
<td>n=2779</td>
</tr>
<tr>
<td></td>
<td>n=1374</td>
<td>n=2360</td>
<td>n=5687</td>
</tr>
<tr>
<td>Age, N (%)</td>
<td>45 (6)</td>
<td>45 (6)</td>
<td>45 (6)</td>
</tr>
<tr>
<td>Women, N (%)</td>
<td>358 (52.7)</td>
<td>647 (51.8)</td>
<td>1581 (54.4)</td>
</tr>
<tr>
<td>Total cholesterol ≥240 mg/dl, N (%)</td>
<td>218 (31.7)</td>
<td>360 (31.1)</td>
<td>535 (18.4)</td>
</tr>
<tr>
<td>LDL cholesterol ≥160 mg/dl, N (%)</td>
<td>229 (37.3)</td>
<td>389 (35.2)</td>
<td>576 (20.3)</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40 mg/dl, N (%)</td>
<td>126 (19.5)</td>
<td>223 (19.5)</td>
<td>470 (16.2)</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>166 (24.6)</td>
<td>384 (30.7)</td>
<td>729 (25.2)</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>49 (7.5)</td>
<td>113 (9.7)</td>
<td>289 (10.0)</td>
</tr>
<tr>
<td>Smoking, N (%)</td>
<td>202 (30.5)</td>
<td>411 (33.2)</td>
<td>934 (32.4)</td>
</tr>
<tr>
<td>Body mass index ≥30, N (%)</td>
<td>103 (15.4)</td>
<td>261 (21.0)</td>
<td>525 (18.1)</td>
</tr>
<tr>
<td>Waist circumference ≥102 or ≥88 cm, N (%)</td>
<td>163 (24.3)</td>
<td>331 (26.7)</td>
<td>256 (7.4)</td>
</tr>
<tr>
<td>Sedentary, N (%)</td>
<td>452 (69.2)</td>
<td>652 (52.9)</td>
<td>1370 (47.1)</td>
</tr>
<tr>
<td>Non-fatal coronary heart disease, N (%)</td>
<td>11 (1.6)</td>
<td>9 (0.7)</td>
<td>37 (5.3)</td>
</tr>
<tr>
<td>Non-fatal cardiovascular disease, N (%)</td>
<td>24 (3.5)</td>
<td>25 (2.0)</td>
<td>75 (10.8)</td>
</tr>
<tr>
<td>Coronary heart disease 10-year mortality, N (%)</td>
<td>1 (0.2)</td>
<td>2 (0.2)</td>
<td>11 (1.6)</td>
</tr>
<tr>
<td>Cardiovascular disease 10-year mortality, N (%)</td>
<td>1 (0.2)</td>
<td>2 (0.2)</td>
<td>20 (2.9)</td>
</tr>
<tr>
<td>All-cause 10-year mortality, N (%)</td>
<td>8 (1.2)</td>
<td>13 (1.0)</td>
<td>102 (14.7)</td>
</tr>
</tbody>
</table>

*Mean (Standard Deviation); HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Fig. 1. Participation and follow-up flow chart. AMI, acute myocardial infarction; CHD, coronary heart disease; CVD, cardiovascular disease; PAD, peripheral artery disease.
Total and LDL cholesterol and smoking were the only cardiovascular risk factors with significant adjusted PAF in those 35 to 54 years old. Adjusted PAF for total, LDL and HDL cholesterol and hypertension was significant in the 55- to 74-year-old age stratum and the whole sample (Table 4).

In participants ages 35–54, the adjusted PAF of CVD was significant for LDL cholesterol [29%; [95% Confidence Interval: 4,54]], HDL cholesterol [23%; (4,43)], and smoking [25%; (2,48)]; in the older group, only HDL cholesterol [13%; (5,22)] and hypertension [37%; (18,57)] had significant adjusted PAF.

In our cohort, all-cause mortality for ages 35–54 was 2.3% and 0.5% for smokers and non-smokers, respectively (P = 0.001). However, this difference was not statistically significant in the older group (13.6% vs. 9.8%, P = 0.100). PAF of all-cause mortality for smokers was 51% and 4% for ages 35–54 and 55–74, respectively.

The marked decrease in mean total and LDL cholesterol between the 1995 and 2005 surveys resulted in lower CHD-PAF for these risk factors in all age groups (Fig. 2).

Discussion

PAF magnitude depends on the effect size of risk factor exposure and on this risk factor's prevalence. Effect size depends in turn on length of follow-up, age group, prevalence in that age group, period of time and region. Our study showed that age group and study period are important determinants of the magnitude of CHD-PAF for total, LDL, and HDL cholesterol, hypertension, diabetes and smoking. In our region, the risk factors with the highest population impact on CHD were smoking and LDL cholesterol in those aged 35–54 years and hypertension, LDL cholesterol and HDL cholesterol for ages 55–74. PAFs for total and LDL cholesterol experienced the most important change as regional prevalence decreased from 1995 to 2005 (Grau et al., 2007). Therefore, PAF should be calculated by age group and periodically by country or region to adequately monitor population risk and identify potential benefits of preventive public health initiatives.

Age and PAF estimates

Elevated LDL cholesterol had the highest potential impact on CHD prevention in our population. PAF estimates from the INTERHEART study of 52 countries and some other local studies showed similar results (Yusuf et al., 2004; Singh-Manoux et al., 2008; Woodward et al., 2008; Emberson et al., 2003). However, our findings differed from an earlier study attributing the highest CHD-PAF in the Spanish population to overweight (Medrano et al., 2007). Risk factor prevalence for that study population was estimated from a meta-analysis that did not consider age groups or differences in survey periods (Medrano et al., 2005). In addition, risk factor prevalence in CHD cases, needed to estimate adjusted PAF, came from a national myocardial infarction registry involving hospitals with a coronary care unit (Reina et al., 2007).

In our cohort, smokers <55 years had significantly higher 10-year risk of developing a CHD event, but also 4 times the risk of non-smokers their age of all-cause mortality. These findings concur with those in a young Swedish cohort, where smoking had the highest impact on CHD (Nilsson et al., 2006). Our cohort also corroborated Schnohr et al., which had shown that PAF of CHD death related to smoking decreased with age (Schnohr et al., 2002). Lloyd-Jones et al. (2006) reported that smokers had CVD much earlier than non-smokers in the Framingham Heart Study. However, lifetime risk for CVD was similar for smokers and non-smokers, due to the competing risk of death from other smoking-related causes (Lloyd-Jones et al., 2006; Mamun et al., 2004), illustrated in our study by increased all-cause mortality in younger participants. The potential benefit of smoking cessation is more evident in middle-aged adults in most world regions, but also exists in older smokers in some populations (Vollset et al., 2006; Baba et al., 2006; Mähönen et al., 2004).

Study periods and PAF estimates

The simultaneous presence of cardiovascular risk factors occurs in both men and women more frequently than could be expected by chance (Ramos et al., 2004), suggesting that modifying any level of exposure may influence other risk factors (Walter, 1976). Therefore, comparing the PAF for different risk factors is only useful to prioritize interventions. Resulting changes in the prevalence of one or various risk factors will then require PAF recalculation (Rowe et al., 2004). This phenomenon is illustrated in our study by the fact that the dramatic decrease in population distribution of total and LDL cholesterol observed in our region (Grau et al., 2007) substantially changed PAF estimates between 1995 and 2005.

Time of follow-up and PAF estimates

The predictive power of cardiovascular risk factors varies slightly over time (Menotti et al., 2005; Menotti and Lanti, 2003) and their maximum effects on mortality may be observed 10 or more years after exposure onset or measurement (Rose, 1982; Tanuseputro et al.,

Table 2 Cardiovascular risk factors at recruitment according to acute myocardial infarction or angina pectoris occurrence, or death from coronary heart disease during follow-up in population of Girona, Spain.

<table>
<thead>
<tr>
<th>Event Variables</th>
<th>35–54 years</th>
<th>55–74 years</th>
<th>35–74 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events during follow-up</td>
<td>Events during follow-up</td>
<td>Events during follow-up</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>p value</td>
</tr>
<tr>
<td>Age*</td>
<td>1877</td>
<td>23</td>
<td>0.07</td>
</tr>
<tr>
<td>Age</td>
<td>45 (6)</td>
<td>47 (5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total cholesterol ≥ 240 mg/dl</td>
<td>553 (31,15)</td>
<td>14 (70,0)</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL cholesterol ≥ 160 mg/dl</td>
<td>594 (35,4)</td>
<td>13 (81,2)</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL cholesterol &lt; 40 mg/dl</td>
<td>328 (18,9)</td>
<td>7 (36,8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>526 (28,1)</td>
<td>14 (63,6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>151 (8,5)</td>
<td>7 (33,3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>588 (31,8)</td>
<td>16 (69,6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Body mass index ≥ 30</td>
<td>349 (18,5)</td>
<td>5 (22,7)</td>
<td>0,59</td>
</tr>
<tr>
<td>Waist circumference ≥ 102 or ≥ 88 cm</td>
<td>476 (25,6)</td>
<td>6 (27,3)</td>
<td>0.86</td>
</tr>
<tr>
<td>Sedentary</td>
<td>1078 (58,7)</td>
<td>12 (57,1)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein. *Mean (Standard Deviation).
In the context of the Framingham Heart Study, obesity was associated with increased relative risk for development of CVD in a population, ages 35–75, followed for 44 years (Wilson et al., 2002). In addition, a meta-analysis has shown that studies with a follow-up longer than 10 years were more likely to observe a significant association between obesity and CHD (Bogers et al., 2007). Therefore, the BMI increase over 10 years in our population (Grau et al., 2007) will take some time to translate into higher myocardial infarction incidence and mortality rates.

**Implications for CHD prevention**

Prevention strategies are usually assessed using different cut-points to define risk factor prevalence. We followed NCEP III recommendations to categorize total and LDL cholesterol for our PAF estimates (Expert Panel National Cholesterol Education Program, 2001). Had we used more recent European guidelines (Fourth Task Force European Guidelines Cardiovascular Prevention, 2007), i.e., total cholesterol <190 mg/dl and LDL cholesterol <115 mg/dl, the prevalence of hypercholesterolemia would have exceeded 86%. We consider it unrealistic to tackle a public health challenge of that magnitude. Indeed, the adaptation of cardiovascular disease prevention strategies to local characteristics is achieved by adopting realistic and feasible aims. When setting therapy thresholds we should take into account that the reduction in absolute risk in Spain was much smaller than in high-incidence countries. At the population scale, this fact involves greater clinical benefit and economic advantages when reducing the risk of CHD in high-incidence countries (Grau and Marrugat, 2008).

Given the factors included in the PAF estimation, a population with many individuals at small risk cannot be distinguished from one with few individuals at high risk. Therefore, cost-effective public health policy must consider relative risk to make that distinction (Walter, 1976; Wacholder et al., 1994).

**Study limitations and strengths**

All PAF estimates in this paper should be interpreted with caution due to several study limitations. First, despite the differences observed in risk factor prevalence by sex (Tanuseputro et al., 2005), we did not stratify the analysis by sex because the low incidence of CHD events observed, particularly in women, was similar to that previously reported in our region (Gill et al., 2007).

Estimation of PAF with a composite CVD end-point would enable broader evaluation of the potential benefits of a comprehensive intervention. Despite the fact that CHD and stroke have some risk factors in common, effect size differs substantially (Kannel et al., 2004). Our cohort also did not include older participants (>74 years) at higher risk of stroke (Marrugat et al., 2007). Therefore, we focused on CHD end-points.

**Table 4**

Age-stratified population attributable fraction of acute myocardial infarction or angina pectoris occurrence, or death from coronary heart disease for various cardiovascular risk factors in population of Girona, Spain, at recruitment.

<table>
<thead>
<tr>
<th></th>
<th>35–54 years</th>
<th>55–74 years</th>
<th>75–84 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAP a 95%CI</td>
<td>RAP b 95%CI</td>
<td>RAP c 95%CI</td>
</tr>
<tr>
<td>Total cholesterol ≥240 mg/dl</td>
<td>55 22,81</td>
<td>45 4,80</td>
<td>18 0,37</td>
</tr>
<tr>
<td>LDL cholesterol ≥160 mg/dl</td>
<td>70 34,86</td>
<td>64 22,87</td>
<td>33 12,54</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40 mg/dl</td>
<td>23 −4,53</td>
<td>−3 −34,28</td>
<td>27 15,40</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 21,76</td>
<td>25 −37,59</td>
<td>50 26,73</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26 4,48</td>
<td>18 −4,44</td>
<td>7 −5,18</td>
</tr>
<tr>
<td>Smoking</td>
<td>55 25,79</td>
<td>64 30,80</td>
<td>2 −5,11</td>
</tr>
<tr>
<td>Body mass index ≥30</td>
<td>5 −16,27</td>
<td>−19 −25,1</td>
<td>5 −10,21</td>
</tr>
<tr>
<td>Waist circumference ≥102 or ≥88 cm</td>
<td>2 −21,29</td>
<td>−10 −34,13</td>
<td>1 −20,21</td>
</tr>
<tr>
<td>Sedentary</td>
<td>−11 −63,49</td>
<td>−5 −63,58</td>
<td>−1 −29,28</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein.

* Model adjusted for sex, age, LDL cholesterol, hypertension, diabetes, and smoking.
* Model adjusted for sex, age, LDL cholesterol, HDL Cholesterol, hypertension.
* Model adjusted for sex, age, LDL cholesterol, HDL Cholesterol, hypertension, diabetes, and smoking.
* Total cholesterol was not adjusted for LDL cholesterol.
The dichotomization of all risk factor exposures might lead to non-differential misclassification (Fourth Task Force European Guidelines Cardiovascular Prevention, 2007, Greenland, 2001). One suggested alternative is to create a gradient of exposure in three or more groups (Hanley, 2001). The anticipated benefits, expressed by PAF, imply that an intervention on cholesterol levels would move all at-risk participants to recommended exposure levels. However, these expectations are probably unrealistic and ignore the limited effect of available dietary controls and high costs of lipid-lowering drugs (Daviglus et al., 2006). To improve our statistical power, we chose cut-points that represented realistic population objectives while preserving the rule that the non-exposed group was in fact likely to be non-exposed (Expert Panel National Cholesterol Education Program, 2001).

Conclusions

Overall, LDL cholesterol levels had the highest potential for CHD prevention over 10 years in a Mediterranean population aged 35–74 years. In age-stratified analyses, PAF estimates were highest for smoking among participants ages 35–54 and for hypertension and low HDL cholesterol among those 55 and older. PAF may require periodic age-stratified recalculation of prevalence to adequately monitor the population trends in world regions.
Conflict of interest statement

The authors declare that there are no conflicts of interest.

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