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Cardiovascular Risk and Physical Activity: Simulated Analysis in General Practice Patients Based on a Risk Score System

Maria Scatigna[1]*, Maria De Felice[1], Anna R. Giuliani[1], Fabio Samani[2], Luigi Canciani[2], Leila Fabiani[1]

[1]Department of Medicine, Health and Environmental Sciences, University of L'Aquila - Italy
[2]Health Search – Italy

Abstract

Aim: This cross-sectional study was aimed at evaluating the association between physical activity (PA), overweight and CV risk in a large sample of Italian general practice patients and forecast the impact of increasing PA in a general population.

Methods: Regression analysis on single CV risk factors and stratification of global risk score have been carried out on 45,862 records with normal/overweight and active/inactive conditions as primary explanatory variables. Moreover a hypothetical attributable risk was calculated on the basis of expected cases.

Results: HDL cholesterol resulted the risk factor most correlated with PA. Systolic blood pressure and fasting plasma glucose levels seemed to be more correlated to overweight than to PA. Active women and men would respectively have a 15% and 17% lower probability of experiencing a major cardiovascular event in the subsequent ten years than their inactive counterparts, adjusting for overweight. If inactive subjects became active at the lowest level, 818.8 cases/100,000 men and 201.5 cases/100,000 women aged 35-69 years would be protected during the same period.

Conclusion: As counsellors for active lifestyle, general practitioners could contribute in reducing the absolute number of CV major events in the 'healthy' general population.

Keywords: CVD risk; Physical activity; General practice

Introduction

Cardiovascular diseases (CVDs), including myocardial infarction and stroke, are the major causes of morbidity, disability and mortality in Italy and were responsible for the deaths of 97,953 men and 126,531 women in 2008. The most important risk factors for these diseases are hypertension, hypercholesterolemia, diabetes, smoking, a sedentary lifestyle, and obesity [1].

Various methods of evaluating cardiovascular risk have been developed, beginning with the American Framingham score [2]. In relation to coronary heart diseases, the Framingham score can be calculated on the basis of age, gender, systolic and diastolic pressure, smoking habits, total cholesterolemia, high-density lipoprotein (HDL) cholesterol, the presence/absence of diabetes, and the electrocardiographic (ECG) presence/absence of left ventricular hypertrophy. Another method of classifying the risk of CVD is the European Systematic Coronary Risk Evaluation (SCORE), in which coloured charts indicate the 10-year risk of subjects aged 40-65 years on the basis of their gender, cholesterol levels, systolic pressure, and smoking status [3].

The individual score used in the Italian Project Cuore not only allows a precise risk estimate (unlike the class estimates used in the charts), but also takes into account continuous values for age, systolic blood pressure, total cholesterolemia and HDL cholesterol, and considers the prescription of anti-hypertensive drugs (yes/no) [4]. The score applies to subjects aged 35-69 years, and indicates the percentage of people of the same age and gender, and with the same characteristics, who are likely to experience a first major cardiovascular event (myocardial infarction or stroke) in the subsequent ten years. This score provides general practitioners (GPs) with an important opportunity to discuss possible preventive action with their patients because it is known that appropriate preventive and clinical interventions can considerably reduce the morbidity and mortality associated with CVD.

Within other risk estimation systems: ASSIGN had the main advantages of the addition of an area indicator of social deprivation and family history of coronary heart disease; QRISK was developed using a substantial amount of data from pooled general practice databases; the Prospective Cardiovascular Munster (PROCAM) function is derived from a relatively small sample; some consider it to be underpowered in women; Reynolds Risk Scores were developed primarily to incorporate C-reactive protein (CRP), wich is now know to be a strong predictor of CVD risk [5].

Physical exercise plays a fundamental role in reducing the risk of coronary disease and all-cause mortality, and has been evaluated in many studies [6-15]. A meta-analysis by Sattelmair et al. showed that, in comparison with no exercise, a minimum of moderately intense physical activity (PA) (150 minutes/week) leads to a 14% reduction in the risk of coronary disease (relative risk [RR] 0.86, 95% confidence interval [CI] 0.77-0.96), and a reduction of 20% (RR 0.80, 95% CI 0.74-0.88) if the exercise is increased to 300 minutes/week) [14]. A review by other authors has shown that high levels of PA play a significantly protective role against coronary disease (RR 0.73, 95% CI 0.66-0.88; $p < 0.00001$), and other studies have shown that an increase in PA or fitness over time reduces mortality due to coronary diseases as well as all-cause mortality [12,16-22].

The aims of this study were: firstly to evaluate the association between PA levels and overweight (as predictors) and CV risk single factors and global score (as health outcomes); secondly to forecast the impact on the general population of a physical inactivity reduction by

***Corresponding author:** Maria Scatigna, Department of Medicine, Health and Environment Sciences, University of L'Aquila, Italy, E-mail: maria.scatigna@cc.univaq.it

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calculating the expected cases of a CV major events and the 'theoretical' attributable risk in a GP population.

Method and Materials

Study design and data source

This cross-sectional study involved a sample of general practice patients observed in 2007. The data were provided by Health Search, a research institute of the Italian Society of General Medicine (SIGM) that was founded in 1998 and is based on a network of researchers who use Millewin© software to manage and record clinical data [23-25]. The GPs regularly send clinical data to a centralised database recognised as containing complete information concerning the main aspects of healthcare information. The geographic distribution of the GPs is homogeneous and a previous study on indicator variables of GPs clinical practice and use of computerised records demonstrated that the patients' population can be considered representative of the Italian population as a whole and the database is not biased by the characteristics of the GPs, so it can be used for research purposes [26].

Outcomes and determinant variables

The variables assessing CV risk factors were considered independently and as part of a score estimating the "absolute global risk" of experiencing a first major coronary or cerebrovascular event within ten years. This score has been calculated on the basis of Project Cuore method, suitable for subjects aged 35-69 years, by means of a mathematical function that included gender, age, systolic blood pressure (SBP), total cholesterol, HDL cholesterol, smoking habits, diabetes, and hypertension treatment [4].

Primary explanatory variables were BMI-based weight category and PA. Using the international body mass index (BMI) cut-off values, the patients were classified as being "underweight/normal weight", "overweight" or "obese" [27]. PA was self-reported by the patients and classified by the GPs at the time of recording using coded examples of the intensity of work and leisure time PA, as established by Millewin© software: *inactive*, at work he/she remains predominantly in a sitting position, with no need to get up (employee, medical, textile worker, etc..) and spents his/her leisure time only in sedentary activities (television, reading, cinema); *low active*, at work he/she stands up or walks a lot, but does not move loads (normal housework, salesman, bartender, postman, etc..) and spents his/her leisure time walking, riding a bike, gardening, bowling, dancing, etc. for less than 4 hours per week; *active,* at work he/she walks and moves loads a lot (heavy housework, painter, bricklayer, laborer, mechanic, etc.) and spents his/her leisure time walking, bicycling, gardening, bowling, dancing, etc. for more than 4 hours per week; *higly active*, at work he/she moves heavy weights (unloader, porter, etc.) and/or practices competitive sports that imply systematic and heavy training.

Sample

The cardiovascular risk score has been calculated on 45,862 patients aged 35-49 years. Data on BMI and PA were available, respectively, only for 41,896 and 37,481 subjects.

Data analysis

The data were processed using Stata/IC 12.1 software.

Separate gender-based multiple regression models were used to analyse four continuous variables (total cholesterol, HDL cholesterol, fasting plasma glucose - FPG and systolic blood pressure - SBP) in terms of the categorical variables of BMI-based weight classification, PA, and age class [28]. This analysis excluded the subjects receiving specific pharmacological treatment (i.e. lipid-lowering treatment for high total and low HDL cholesterol, anti-diabetic treatment for high FPG, or anti-hypertensive treatment for high SBP).

Mean individual scores and their 95% confidence intervals were calculated in the different BMI-based weight classification and PA categories and Student's t-test was used to verify the significance of the differences.

Subsequently, assuming that, in the worst scenario, the patients' overweight doesn't decrease and PA habits doesn't improve in the following ten years, the calculation of absolute number of foreseeable cases was simulated on the basis of the individual scores. Using this approach we estimated the hypothtical relative risk (RR) of exposure to the different levels of PA (low-active *vs* inactive; active/high active *vs* inactive) relating to 37,015 records, adjusting by BMI-based weight category (Mantel-Haenszel stratification and the chi-squared test). Finally, also the hypothetical population attributable risk (AR) was calculated.

Using the information from Palmieri et al. study cohort about the level of SBP, Total and HDL cholesterol as quantitive variables and considering the whole sample size for the calculation, the study power resulted higher than 80% [4].

The database complies with European Union guidelines on the use of medical data for medical research. The protocol of this study was approved by the Scientific and Ethical Advisory Board of Health Search.

Results

Comparison of the four multiple regression models showed that, taking into account the simultaneous effect of age, HDL cholesterol seemed to be correlated to overweight and PA (Table 1). In comparison with the normal weight subjects, the overweight and obese males showed an estimated reduction in HDL cholesterol levels of 4.97 mg/dL ($p < 0.001$) and 8.37 mg/dL ($p < 0.001$), and the overweight and obese females showed reductions of 5.48 mg/dL ($p < 0.001$) and 9.57 mg/dL ($p < 0.001$). In comparison with the inactive subjects, the estimated increase in HDL cholesterol was 0.40 mg/dL (n.s.) in low-active males, and 1.92 mg/dL ($p < 0.01$) in active/high active males; the corresponding values for the females were 0.28 mg/dL (n.s.) and 1.38 mg/dL ($p < 0.001$).

Weight had a significant influence on FPG levels in both genders: an estimated increase in overweight and obese males of respectively 2.93 mg/dL ($p < 0.001$) and 7.05 mg/dL ($p < 0.001$), and in overweight and obese females of respectively 3.59 mg/dL ($p < 0.001$) and 7.78 mg/dL ($p < 0.001$). FPG seemed not to be significantly correlated with PA both in males and in females.

Among the overweight and obese subjects, there were significant increases in SBP of respectively 3.29 mmHg ($p < 0.001$) and 6.91 mmHg ($p < 0.001$) in males, and respectively 3.71 mmHg ($p < 0.001$) and 7.79 mmHg ($p < 0.001$) in females. As for FPG, no-significant association has been found between SBP and PA.

In the total cholesterol model, age seemed to be the most important variable, particularly among the women: in comparison with the reference age group (35-39 years), the estimated increases in the three subsequent age groups were 10.00 mg/dL ($p < 0.001$), 27.00 mg/dL ($p < 0.001$) and 31.10 mg/dL ($p < 0.001$). This trend was not found among the males: the corresponding increases were 9.66 mg/dL ($p < 0.001$), 12.79 mg/dL ($p < 0.001$) and 5.93 mg/dL ($p < 0.001$). In respect to the weight

Dependent variables	Total cholesterol[1] (mg/dL)		HDL cholesterol[1] (mg/dL)		FPG[2] (mg/dL)		SBP[3] (mmHg)	
Independent variables	β coeff	P value	β coeff	P value	β coeff	P value	β coeff	P value
Males								
BMI								
Overweight vs normal weight	3.93	***	-4.97	***	2.93	***	3.29	***
Obese vs normal weight	-0.13	n.s.	-8.37	***	7.05	***	6.91	***
Physical activity								
Low active vs Inactive	1.59	*	0.4	n.s.	-0.18	n.s.	-0.05	n.s.
Active/High active vs Inactive	3.82	***	1.92	**	-0.45	n.s.	0.23	n.s.
Age								
40-49 vs 35-39 years	9.66	***	1.01	***	2.75	***	0.83	n.s.
50-59 vs 35-39 years	12.79	***	1.92	***	6.71	***	2.96	***
59-69 vs 35-39 years	5.93	***	2.75	***	10.12	***	5.79	***
No.	16,621		16,621		15,404		10,762	
R^2	1.4%		7.0%		7.1%		5.9%	
F test	***		***		***		***	
Females								
Weight								
Overweight vs normal weight	3.9	***	-5.48	***	3.59	***	3.71	***
Obese vs normal weight	-0.28	n.s.	-9.57	***	7.78	***	7.79	***
Physical activity								
Low active vs Inactive	1.05	n.s.	0.28	n.s.	0.06	n.s.	-0.24	n.s.
Active/High active vs Inactive	1.77	*	1.38	***	-0.26	n.s.	0.69	n.s.
Age								
40-49 vs 35-39 years	10.00	***	0.06	n.s.	2.35	***	3.86	***
50-59 vs 35-39 years	27.00	***	0.81	*	5.45	***	8.94	***
59-69 vs 35-39 years	31.10	***	0.75	n.s.	8.4	***	13.1	***
No.	18,029		18,029		17,636		12,218	
R^2	8.5%		7.4%		9.9%		14.5%	
F test	***		***		***		***	

Table 1: Multiple regression analyses on four biological dependent variables by age, BMI and physical activity in GPs' patients
* = p < 0.05, ** = p< 0.01, *** = p < 0.001
Analyses carried on patients: 1Not receiving lipid-lowering treatment; 2Not receiving anti-diabetic treatment; 3Not receiving anti-hypertensive treatment
HDL = High-Density Lipoprotein, **FPG** = Fasting Plasma Glucose, **SBP** = Systolic Blood Pressure

status, cholesterol seemed more associated with overweight (males 3.93 mg/dL, p < 0.001; females 3.90 mg/dL, p < 0.001) than with obesity (males -013 mg/dL, n.s.; females -0.28 mg/dL, n.s.). There was also an apparently non-protective trend in the case of PA: in comparison with the inactive patients, the males active/high active had a total cholesterol level that was 3.82 mg/dL higher (p < 0.001), and the female's low-active had a level that was 1.77 mg/dL higher (p < 0.05).

The mean expected number of major cardiovascular events per 100 patients in the subsequent ten years was 9.20 (95% CI: 9.09-9.31) among men, and 3.25 (95% CI: 3.21-3.30) among women. Comparing PA categories, emerged a significant difference between inactive and active/high active patients, higher in men (about two expected events, 9.84 *vs* 7.86, p < 0.001) than in women (about one expected event 3.46 *vs* 2.67 and 1.63, p < 0.001) (Table 2).

The differences between the BMI-based weight categories were more marked in the patients of both genders: more than four expected cases between the obese and normal weight in males (11.20 *vs* 6.99, p < 0.001) and two cases and a half in women (4.64 *vs* 2.15, p < 0.001) (Table 2).

Table 3 and Figure 1 show the results of the simulated analysis based on expected number of major events in the next 10-years by PA levels. Only the active/high active sub-group had a significantly lower 'theoretical' risk than the inactive sub-group, with an RR of 0.76 (95% CI 0.60-0.98) among the females and 0.80 (95% CI 0.71-0.90) among the males. That is to say, in the absence of an active style improvent in the

Expected percentage of cases over 10 years	Males	Females
No.	17,948	19,533
No physical activity	9.84 (9.62-10.06)	3.46 (3.38-3.54)
Light physical activity	9.61 (9.42-9.81)	3.19 (3.11-3.27)
Moderate/intense physical activity	7.86 (7.65-8.08)	2.67 (2.56-2.78)
No.	20,012	21,884
Underweight/normal weight	6.99 (6.80-7.18)	2.15 (2.10-2.21)
Overweight	9.38 (9.21-9.54)	3.65 (3.57-3.74)
Obese	11.20 (11.10-11.61)	4.64 (4.53-4.76)

Table 2: Cardiovascular risk score by physical activity and BMI: mean values and 95% confidence intervals.

sample, it is estimated that active/high active women and men would respectively have a 23% and 20% lower probability of experiencing a major cardiovascular event. If the additional effect of overweight is taken into account, this protective effect decreased as the overweight-adjusted RR was 0.85 (95% CI 0.66-1.01) among the women and 0.83 (95% 0.73-0.94) among the men (i.e. active/high active women and men would respectively have a 15% and 17% lower probability of experiencing a major cardiovascular event). Furthermore, the Mantel-Haenszel analysis showed that stratifying variable was not statistically significant, and so the protective effect of an active/high active lifestyle was maintained in the overweight and obese subjects.

In terms of impact, the population RA was 6.2% (p < 0.05) among the women and 8.9% (p < 0.001) among the men. Given the estimated

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	Females				Males			
	Crude relative risk			Population attributable risk	Crude relative risk			Population attributable risk
	RR	95% CI			RR	95% CI		
Inactive	1				1			
Low active	0.927	0.786	1.094	3.7 %	0.977	0.879	1.085	1.3 %
Active / High active	0.765	0.597	0.981	6.2 %	0.800	0.707	0.906	8.9 %
	Stratified RR				Stratified RR			
	RR	IC 95			RR	IC 95		
Inactive	1				1			
Low active	0.980	0.931	1.157		0.998	0.899	1.109	
Active / High active	0.847	0.660	1.088		0.829	0.732	0.939	

Table 3: Hypothetical relative risk and population attributable risk of cardiovascular major events by physical activity level. Crude RR and RR stratified by BMI-based weight classification (Mantel-Haenszel method).

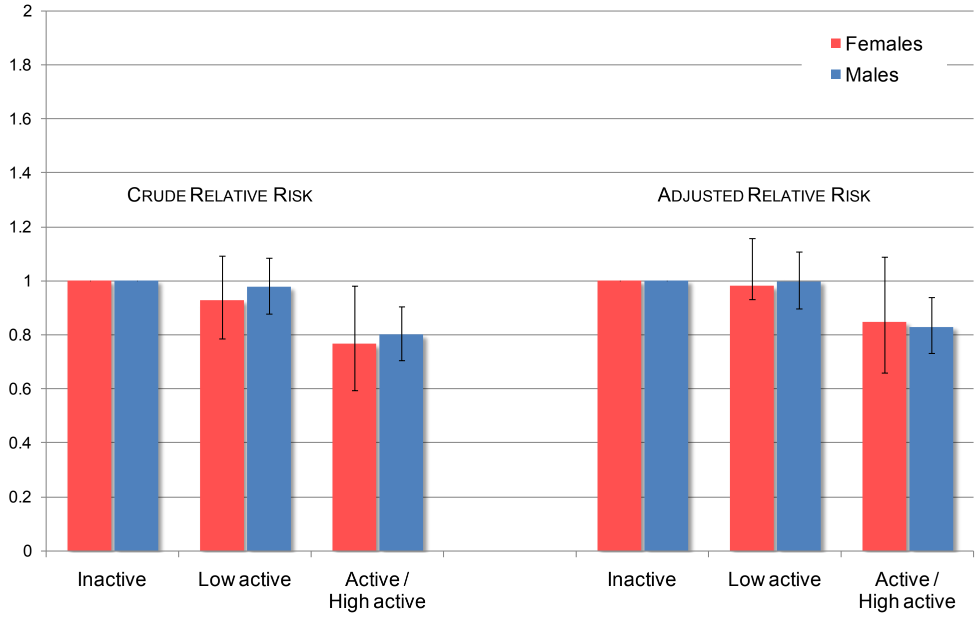

Figure 1: Hypothetical relative risk of cardiovascular major events by physical activity level, Crude RR and RR stratified by BMI-based weight classification (Mantel-Haenszel method).

10-year incidence of 9.20 cases per 100 men and 3.25 cases per women, it can be calculated that, if the inactive subjects became active/high active, 818.8 cases/100,000 men and 201.5 cases/100,000 women aged 35-69 years would be saved in the same period.

Discussion

In comparison with the data of the surveillance national study 'Progressi delle Aziende Sanitarie per la Salute in Italia' (PASSI) which used computer-assisted telephone interviewing (CATI) in a national sample of about 15,000 subjects, our sample had a higher prevalence of diseases in the corresponding age classes: 10% higher in the case of overweight/obesity, 6% higher in the case of hypertension, and about twice as high in the case of diabetes [29,30]. Furthermore, the percentage of current smokers was lower and the percentage of ex-smokers higher, probably because they had stopped smoking after the occurrence of clinical events, the diagnosis of disease or medical counselling [29]. Hinrichs et al. have confirmed that GPs behave differently in terms of recommending PA, and tend to concentrate more on educating patients with chronic diseases [31].

However, despite the limitations described above, our findings are useful because our sample was larger than that of the PASSI study. Furthermore, unlike our study, the PASSI study used self-reported data based on patient's recall rather than laboratory data or medical diagnoses also for the clinical variables, and for this reason, there may be a selection bias insofar as more healthy participants are probably more willing to respond to a questionnaire.

The patients in our sample did not engage in much PA, particularly the women: less than a quarter of the study sample (22.2%) was active/high active (15.8% of the women, and 29.3% of the men).

It is necessary to point out a methodological limitation relating to the assessment of PA, which was based on the GPs' skill in categorisation on the basis of the patients' self-reports, and not evaluated about its reliability and validity.

Self-reported PA measures have many sources of measurement error due to the cognitive tasks associated with recall, incomplete ascertainment across the spectrum of intensity and physical activity contexts, and possibly the tendency to provide socially desirable responses For that, researchers have long sought alternative measurement approaches by means of technological devices that directly measure human movement (e.g. pedometers, accelerometers).

Nevertheless, these devices have their own set of limitations and sources of measurement error, and there are specific times and circumstances in which self-report measure of PA remains the most appropriate approach, particularly in the context of surveillance and public health [32]. For example, in our study, the formulation of the PA category for the assessment corresponds exactly to the health education message (simple and understandable) that GPs should use to communicate reccomandation about PA healthy levels to the general population and that he/she should assess.

A further limitation in the present study is that ins't possible to know for sure when the data on CVD risk factors, PA and weight status have been collected, since the practitionnairs update the database in a continous way. For example, exposure data (PA) could have been collected after CVD risk factors and not before, or simultaneously. So, we can't exclude that the patient could change his/her behaviour after the GP's counselling due to the risk awareness. But that is a advantage condition that should be considered as confirming condition of our results: that means that the preventable cases could be more that those calculated since a portion could have been hidden by an inducted increasing of PA level.

The regression analyses (Table 1) showed that HDL cholesterol was more clearly associated with PA (particularly in men) and overweight status (particularly in women) than the other intermediate risk factors: the models for total cholesterol, FPG and SBP seemed to be less clear and sometimes contradictory. The meta-analysis of Kelley et al. also found that PA had a greater effect on HDL cholesterol, although it revealed a significant effect on all blood lipids. In the same way the results of the study of Parraga-Martinez et al. will provide extremely useful information about the effectiveness of the proposed strategy (counselling and lifestyles as PA) of improving compliance in the prevention and management of cardiovascular disease based on increased control of lipid profile plasma levels [33,34]. Conversely, Liira et al. demonstred that PA had no effect on HDL cholesterol or other cardiovascular outcomes [35]. Overweight seems to have a transversal effect on all of the parameters, probably because it is less subject to errors and dishomogeneity as it is directly measured in the GPs' surgeries in order to calculate the patients' BMI.

The trend of total cholesterol is inconsistent between genders, and the greatest difference was observed when comparing the youngest age group (35-39 years) with those above the age of 50 years in females: the tripling in levels is probably related to the hormonal changes that occur after menopause. It cannot be excluded that the models of total cholesterol may have involved inverse causality due to the partially clinical/diagnostic character of the GP data (i.e. patients may have been more active because they received GP counselling to reduce a high level of total cholesterol).

Aadahl et al. also found that, unlike other parameters (e.g. diastolic pressure, overweight, waist circumference), SBP was not significantly affected by a change in the level of PA [36]. However, the absence of any apparent protective effect of PA on SBP may also be due to limitations in the method of data collection method: e.g. the lack of information about 'spontaneous' or everyday activities (work, domestic chores) previously pointed out by Churilla and Ford [37]. Furthermore, the published studies describing reduced hypertension levels in more physically active subjects were longitudinal and/or experimental, and compared the effects using dose-response analyses and more precisely defined thresholds for the intensity and frequency of exercise [38,39]. In the same way, we couldn't adjust the PA influence by nutritional intakes as in major studies on diabetes risk [40]. Those might be the reasons for the absence of significance in the regression terms about SBP and FPG.

Moreover in present study, no information about family history of diabetes was available. Again, this limit could explain the poor relationship between impairment in glycemic control and PA, since Ciccone and coll highlighted that family history of diabetes accounts for an increase in cardiovascular risk of individuals even if such subjects have no signs of pre-diabetes or diabetes. It should be interesting to study the role of PA in reducing the hidden risk attributable to that genetically determined condition and potential mediating mechanisms involving other CV risk factors [41].

The hypothetical risk reduction attributable to moderate/intense PA in our simulated analysis (15% in men and 17% in women) is comparable with that found by Sofi et al., although these authors considered a specific disease category (coronary diseases) and activity (leisure time activity): 27% for intense activity *vs* none, and 12% for moderate activity *vs* none [12]. Although the hypothetical RR and AR calculated on the basis of PA are not so high, it needs to be borne in mind that PA/inactivity is a risk factor that concerns everyone in the population and, as in the case of nutritional epidemiology (everyone eats, and the consumption of certain foods and nutritional intake is transversal), even small variations in such risk indices correspond to a high number of cases in absolute terms (and a considerable cost for national health services).

Moreover, the absolute number of preventable cases in the general 'healthy' population would be higher.

An approach very similar to our simulated risk calculation has been recently used by Mallaina and coll in a study predicting the impact of smoking cessation in term of cardiovascular risk reduction in a wide European sample, carried-out, exactly as ours, with a cross-sectional data collection and in the primary care setting [42].

Our study, it should be clear, only gives clues to aetiological factors, without any intention to confirm the causal associations, since it has a cross-sectional design, not longitudinal. By using the CV risk score (with an algorithm based on a previous Italian cohort study) we simply forecasted how many expected cases of CV major events probably could be avoided in the GPs population, while a huge amount of scientific literature focuses on second-level healthcare facilities (specialist).

It is a demonstration of the usefulness of data collection on behavioural risk factors in the general medical practice and highligths the strategic role of GPs as observators, counsellors and, so, as public health promoters.

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Ethical Approval

Health Search, a research institute of the Italian Society of General Medicine (SIGM).

Competing Interests

The Author's declare that they have no competing interests.

Author's contribution statement (individual contribution to the manuscript)

Maria Scatigna took part in study designing, performed the statistical analysis and drafted the manuscript; Maria De Felice contributed to analysis and interpretation of data, drafted the manuscript and revisited it critically for plausibility of clinical content; Anna R. Giuliani took part in the sequence alignment and revisited manuscript critically for epidemiological content; Fabio Samani contributed to acquire data from Health Search Institute and gave final approval of the manuscript; Luigi Canciani contributed to acquire data from Health Search Institute and critically revisited manuscript for epidemiological content; Leila Fabiani conceived the study, participated in designing and coordinated the manuscript.

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