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# Burden of Cardiometabolic Risk Factors on Cerebrovascular Events in a Southern Italian Population

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## Abstract

**Background:** Stroke is the second leading cause of death in the world and the third due to disability. However, there are few data available that identify the risk factors associated with it and their weight in different populations (population risk). **Aim:** Contribute to the knowledge of burden risk factors in stroke in a large cohort of Southern Italy. **Methods**: The data refer to a randomized Campania cohort of 1200 subjects (35 - 74 years) enrolled in 2008-09. Ten years later (2018-19) they were re-evaluated. We analyzed data from 32 patients who reported a cerebrovascular event (stroke or TIA) with the event-free group of subjects (804 subjects: 378 men and 426 women). We evaluated: absolute risk, Odds Ratio (OR), Additional Risk (AR), Risk Attributable to the Population (PAR) and, finally, the Population Attributable risk Fraction (FAP). **Results:** In the comparison between the two groups (patients with events and patients without events) the risk factors with statistically significant differences were: age, Systolic Blood Pressure (SBP), BMI, cholesterol, triglycerides, glycemia and hyperinsulinemia. The ORs with the greatest impact were: blood glucose (5.1), BMI (3.3) and BPS (2.9). Linear regression analysis identified Glycemia and BMI as the only independent variables. The FAPs with the greatest impact were SBP (47.4%) and BMI (42.6%). **Discussion and Conclusions**: Our data confirm that the high incidence of stroke in Campania is particularly related to the high prevalence of obesity and hypertension. In the single patient, however, the risk factors with the greatest impact are: glycaemia BMI an SBP.

## Keywords

Cerebrovascular Risk Factors, Southern Italy, Risk Attributable to the Population

## 1. Introduction

Cardio-Cerebrovascular (CCV) disease remains a major cause of premature mortality and rising health care costs [1] [2]. Particularly stroke is the second leading cause of death worldwide and the third leading cause of disability [3]. For this reason, Cerebrovascular (CV) events have long been considered an important problem of Health public. Consistent and systematic long-term analysises are essential to guide public policy and provide benchmarks for decision makers. The INTERSTROKE study [4] showed that ten risk factors are related to 90% of the risk of stroke. The European guidelines on cardiovascular disease prevention highlight the importance of local epidemiological investigations to target prevention actions [5]. A careful analysis of risk factors is essential. Numerous researchers have studied the odds ratio of risk factors [6] [7] [8], but few have identified the impact of risk factors in the population (Population Attributable risk Fraction), which is undoubtedly more useful for planning interventions in the territories. This work is a contribution to the knowledge of the distribution of risk factors and their burden on the population in an area of the Campania Region. This data seems particularly useful in that, precisely in Campania, there is the highest incidence of stroke, especially in women [9] [10].

## 2. Methods

The data was collected from the internal database of the "VIP project—Valle dell'Irno Prevention". Vip Project is a program of epidemiology and primary prevention of cardiovascular diseases [11] [12]. It is part of the CINDI program (WHO) [13] and is contributing their data to the "Global Burden of Metabolic Risk Factors of Chronic Diseases" [14]. The baseline was carried out in 2008-2009 by means of a cross-sectional survey on a cohort of 1200 men and women aged between 25 and 74 (120 males and 120 females for each decade). The sample was chosen randomly among the residents of Baronissi and Mercato S. Severino and was examined by adopting standardized methodologies recommended by the MONICA Project and Cardiovascular Epidemiological Observatory [15]. Informed consent was obtained from all participants and the study was approved by the local Ethic Committee.

All patients underwent a physician-administered medical history, clinical examination, electrocardiogram (ECG), psychological assessment, and laboratory assessment of vascular risk factors. Blood samples were obtained, after an overnight fasting, from the antecubital vein of the arm, without venous congestion. To calculate Body Mass Index (BMI), we measured height (in meters, using a wall altimeter) and weight (in kilograms using a floor balance, Slimtronic Rowenta®) while subjects wore light clothes. Blood pressure was measured following the criteria of the World Health Organization, therefore the values were obtained by the mean of two consecutive determinations in the right arm after five minutes sitting rest each.

Total and HDL cholesterol, triglycerides, uric acid, C Reactive Protein (CRP) and glycemia were determined by enzymatic method. LDL cholesterol was calculated with Friedewald equation. Insulinaemia was determined by immune enzymatic fluorescence (AIA 21). Creatinine concentrations was measured using the kinetics-plugged method (500 nm) on Cobas-ABX automatic line, while C3 by the nephelometric method on QM 300 method.

Follow up: Ten years later (2018-19), all subjects were contacted by letter or phone. For those who were not able to contact, we have obtained information through family physicians.

The collected data were matched with deterministic method (surname, first name, date of birth, phone number), with hospital discharge records and cards RENCAM. We collected data on 1175 people: 587 men and 588 women. Lost to follow-up were 25. The variables studied included cardiovascular mortality and morbidity (ICD-10 codes: 120 - 125 and 160 - 169). The full description of the measurement techniques has been published previously [10].

We analyzed and compared the data of 32 patients (16 men and 16 women) who had an ischemic brain accident (ischemic stroke and TIA) with the cohort of subjects who did not develop any events (804 subjects: 366 men and 438 women). Subjects with unclearly classifiable events were excluded. Furthermore, in order to have a completely event-free control group, we also excluded subjects with cardiovascular events from the analysis (STEMI, NSTEMI, Angina, myocardial revascularization interventions, etc.). The event had to be proven by clear documentation: medical records from another hospital, data provided by the family doctor, documentation provided by the patient (medical report), documentation found in the RENCAM (Causes of Death of Campania).

The risk factors considered were: diabetes (glycaemia ≥ 126 mg/dl), arterial hypertension (≥140 mm Hg for systolic pressure ≥90 mm Hg for diastolic pressure), obesity (body mass index ≥ 30 kg/m$^2$) hypercholesterolemia (cholesterol serum ≥ 240 mg/dl), hypertriglyceridaemia (triglycerides ≥ 150 mg/dl), hyperuricaemia (uric acid ≥ 6 mg/dl) and metabolic syndrome (ATP III criteria ≥ 3).

## 3. Statistical Analysis

For statistical analysis we used SPSS version 20 software. For each risk factor we calculated:

- Prevalence;
- Absolute Risk;
- Odds Ratio;
- Additional Risk = risk of exposure to the risk factor – risk of not being exposed;
- Risk Attributable to the Population (PAR) = (Additional risk * Prevalence);
- Population Attributable risk Fraction (FAP) = (PAR/total disease incidence).

Comparisons between means were performed using Student's t-test, prevalence comparisons using Chi-squared, and Fisher's exact test. Finally, linear regression analysis (step by step) was used to determine which of the variables under consideration remained significant when all variables were considered simultaneously.

## 4. Results

The incidence of CV ischemic events (stroke and TIA) was 3.8%/year. In both sexes, the events increased with age. Strokes were more common in males, while TIAs were more common in females. In the comparison between the two groups (patients with events and patients without events) there was a statistically significant difference (Table 1) for: age, Systolic Blood Pressure (SBP), body mass index (BMI), cholesterol, triglycerides, glucose and hyperinsulinemia. In all cases (except for HDL-cholesterol) the mean values of the variables under examination were higher in the group of subjects with brain events.

In the linear regression analysis, the only variables that maintained statistical significance were glycaemia (beta = 0.210; P = 0.000) and BMI (beta = 0.132; P = 0.001).

Finally, for all risk factors assessed (Table 2) we reported (adjusted for age): odds ratio, additional risk, prevalence, PAR and FAP. The odds ratios with the largest index were: blood glucose (5.1), BMI (3.3) and SBP (2.9). In contrast, the FAPs with the greatest impact were SBP (47.4%) and BMI (42.6%).

## 5. Discussion and Conclusions

In this work we considered only cardiometabolic risk factors and we did not take

**Table 1.** Comparison of risk factors means values in patients with cerebrovascular events (Stroke and TIA) with the control group.

| Risk Factors | Events (32 subjects) | Control (804 subjects) | P value |
|---|---|---|---|
| Age (years) | 61 ± 10 | 53.2 ± 11.4 | 0.000 |
| Systolic blood pressure (mm Hg) | 146.7± 23.9 | 136 ± 18.9 | 0.002 |
| Diastolic blood pressure (mm Hg) | 87.8 ± 11.8 | 84.6 ± 9.9 | NS |
| Body Mass Index (kg/m$^2$) | 31.8 ± 6 | 28.5 ± 4.5 | 0.000 |
| Cholesterol (mg/dL) | 222.9 ± 58.5 | 205 ± 41 | 0.018 |
| LDL (mg/dL) | 141.2 ± 50.7 | 132.2 ± 37.7 | NS |
| HDL (mg/dL) | 44.8 ± 11.9 | 43.8 ± 10.7 | NS |
| Triglycerides (mg/dL) | 196 ± 118.6 | 146.7 ± 82 | 0.002 |
| Glycaemia (mg/dL) | 143.1 ± 66.4 | 106.2 ± 29.7 | 0.000 |
| Insulin (µlU/ml) | 16.5 ± 23.5 | 10.7 ± 9.3 | 0.006 |
| White blood cells (10$^3$/dL) | 7.0 ± 1.8 | 6.3 ± 1.7 | NS |
| Fibrinogen (mg/dL) | 280.6 ± 75.6 | 282.4 ± 75.2 | NS |
| Platelets (10$^3$/dL) | 207.5 ± 41.1 | 213.6 ± 54.5 | NS |
| $C_3$ (mg/dL) | 118.6 ± 31.5 | 105 ± 34.2 | NS |
| Creatinine (mg/dL) | 0.90 ± 0.2 | 0.90 ± 0.2 | NS |
| Smokers (%) | 15.6% | 23.7% | NS |

**Table 2.** Burden of risk factors for cerebrovascular events. Values corrected for age.

| Risk Factors | Odds Ratio | Confidence Interval 95% | | Additional Risk % | Prevalence | RAP | FAP |
|---|---|---|---|---|---|---|---|
| | | Minimum | Maximum | | | | |
| Systolic blood pressure ≥ 140 mm Hg | 2.9 | 1.3 | 6.3 | 3.7 | 48.0 | 1.8 | 47.4 |
| Body Mass Index ≥ 30 kg/m$^2$ | 3.3 | 1.6 | 6.9 | 4.7 | 34.6 | 1.62 | 42.6 |
| Triglycerides ≥ 150 mg/dL | 2.5 | 1.2 | 5.3 | 3.5 | 38.2 | 1.3 | 35.2 |
| Glycaemia ≥ 126 mg/dL | 5.1 | 2.4 | 10.8 | 9.4 | 13.5 | 1.3 | 34.2 |
| Diastolic blood pressure ≥ 90 mm Hg | 1.9 | 0.9 | 3.8 | 2.4 | 38.3 | 0.9 | 24.2 |
| Cholesterol ≥ 240 mg/dl | 2.1 | 1 | 4.5 | 3.3 | 20.5 | 0.7 | 18 |
| Uric Acid ≥ 6 mg/dL | 1.4 | 0.5 | 3.8 | 1.3 | 14.6 | 0.2 | 5 |

Additional risk (Risk of the exposed − Risk not exposed). RAP = Attributable Population Risk (Additional Risk * Prevalence). FAP = Population Attributable Risk Fraction (RAP/Total Disease Incidence).

into account atrial fibrillation (one of the main determinants of ischemic stroke) since, reviewing patients only after 10 years, we did not have reliable information on rhythm disturbances. Furthermore, the event group is made up of only 32 subjects. But despite this we believe that our work offers numerous points for discussion.

The odds ratio of CCV risk factors is particularly useful in assessing the overall risk of the individual patient. Conversely, for the preventive intervention program in a community, the Population Attributable risk Fraction assumes a primary rule as it expresses the weight of the risk factors in a community.

In our study, the odds ratio values with the greatest impact are: age (as expected), blood glucose (OR 5.1), BMI (OR 3.3) and SBP (OR 2.9). We also found statistically significant differences in the comparison between the event group and the event free group for the following factors: age, SBP, BMI, cholesterol, triglycerides, glycemia. Linear regression, however, showed statistically independent significance for blood glucose and BMI only. Unexpectedly, the HSP loses significance, presumably due to the burden that BMI takes on our population.

A large number of prospective studies have examined the relationship between obesity and stroke [16]. A meta-analysis found a not linear association between BMI and mortality [17]. Over the BMI range of 25 to 50 kg/m$^2$, each 5 kg/m$^2$ increase in BMI was associated with a 40% increase in the risk of stroke mortality; in the lower BMI range (15 to 25 kg/m$^2$), there was no relationship between BMI and stroke mortality. There are also numerous studies on blood glucose that have shown a direct correlation with stroke; in particular, glucose abnormalities, type 2 diabetes or impaired glucose tolerance are common in stroke patients and compromise their prognosis [18] [19] [20] [21] [22]; even more interesting are the works that show how important the therapeutic choice and optimization of the same to reduce stroke are in the diabetic [23] [24].

Although (age-standardized) stroke mortality rates have declined worldwide over the past few decades, the absolute figures are still not comforting. The number of people affected, the number of non-survivors and the global social impact (DALY lost) still remain high [25]. In the Mediterranean areas and especially in Italy, the incidence of cardio-cerebrovascular diseases is lower than the incidence observed in other areas of Europe and in the United States [26] [27], but even in this case the absolute numbers are not acceptable. Also, in some areas of the Mediterranean there are areas with a very high incidence of cardiovascular diseases. This also applies to the Campania region [27], which has the highest incidence rate of stroke. Furthermore, a study by the Higher Institute of Health (Istituto Superiore di Sanità) has indicated Campania as the Italian region with the highest rate of deaths from preventable cardio-cerebrovascular diseases [27]. This figure reflects inadequate prevention programs and a high number of avoidable deaths [28]. In planning interventions in the population, data relating to the prevalence of risk factors and FAP are necessary. However, these data are scarce in the literature and for this reason our data suggest food for thought. In the Mediterranean area, interventions on the prevention of Stroke should give greater attention to systolic arterial hypertension and obesity. The percentage of disease attributable to these two risk factors is respectively 47.4% and 42.6%. Particular attention should also be paid to hypertriglyceridemia (35.2%) and diabetes (34.2%), although the burden of diabetes in terms of... is reduced due to the low prevalence in the population, compared to other factors of risk. In conclusion, while the odds ratio and linear regression help us understand the role of risk factors in influencing the development of the disease in the individual patient, RAP and FAP allow us to better interpret the impact of risk factors in entire population. There is ample evidence that effective action on risk factors reduces events. Therefore, it is important to sensitize health professionals in order to consider epidemiological data among the essential tools to optimize their intervention strategies on the population.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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