Int J Public Health (2017) 62:775–786
DOI 10.1007/s00038-017-0993-2

ORIGINAL ARTICLE

Impact of preventable risk factors on stroke in the EPICOR study: does gender matter?

Slavica Trajkova[1] · Angelo d'Errico[2] · Fulvio Ricceri[1,2] · Francesca Fasanelli[1] · Valeria Pala[3] · Claudia Agnoli[3] · Rosario Tumino[4] · Graziella Frasca[4] · Giovanna Masala[5] · Calogero Saieva[5] · Paolo Chiodini[6] · Amalia Mattiello[7] · Carlotta Sacerdote[1] · Salvatore Panico[7]

Received: 27 February 2017 / Revised: 9 May 2017 / Accepted: 12 June 2017 / Published online: 22 June 2017

Abstract
Objectives The effect of modifiable stroke risk factors in terms of prevented cases remains unclear due to sex-specific disease rate and risk factors prevalence. Our aim was to estimate their impact on stroke by gender through population-attributable fraction (PAF), preventive fraction (PF) and their combination in EPIC-Italian cohort.
Methods 43,976 participants, age 34–75, and free of cardiovascular disease at baseline (1993–1998) were followed up for almost 11 years. Adjusted hazard ratios and PAF were estimated using Cox models.
Results We identified 386 cases. In males, the burden for stroke was 17% (95% CI 4–28%) for smoking and 14% (95% CI 5–22%) for alcohol consumption. In females, hypertension was carrying the biggest burden with 18% (95% CI 9–26%) followed by smoking 15% (95% CI 7–22%). Their combination was 46% (95% CI 32–58%) in males and 48% (95% CI 35–59%) in females. PF for current smokers was gender unequal [males 21% (95% CI 15–27%) females 9% (95% CI 1–17%)].
Conclusions Half of strokes are attributable to potentially modifiable factors. The proportion of prevented cases is gender unbalanced, encouraging sex-specific intervention.

Keywords Stroke · Gender medicine · Risk factors · Cohort study · Population-attributable fraction · Preventive fraction

Joint last authors: Carlotta Sacerdote and Salvatore Panico

Electronic supplementary material The online version of this article (doi:10.1007/s00038-017-0993-2) contains supplementary material, which is available to authorized users.

✉ Carlotta Sacerdote
carlotta.sacerdote@cpo.it

[1] Unit of Cancer Epidemiology, Department of Medical Sciences, University of Turin and Città della Salute e della Scienza University-Hospital Center for Cancer Prevention (CPO), Turin, Italy

[2] Unit of Epidemiology, Regional Health Service, Grugliasco, Turin, Italy

[3] Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[4] Cancer Registry, Department of Prevention, ASP, Ragusa, Italy

[5] Cancer Risk Factors and Lifestyle Epidemiology Unit Cancer Research and Prevention Institute-ISPO, Florence, Italy

[6] Department of Physical and Mental Health and Prevention, Second University of Naples, Naples, Italy

[7] Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

Introduction

Stroke is the second leading cause of death in Europe (Lozano et al. 2012) and the third worldwide (Wang et al. 2015). Even if between 2005 and 2015 was noted a reduction of the mortality rates due to cerebrovascular diseases, stroke is still among the top three causes of years of life lost (YLL), and among with ischemic heart disease are the two leading causes for premature mortality globally (Wang et al. 2015).

The majority of strokes occurred in people with potentially modifiable multiple risk factors such as behavioral (smoking, physical inactivity, high alcohol consumption, and poor diet), pathophysiological (atrial fibrillation, coronary artery disease, and diabetes), cluster of metabolic factors (obesity, hypertension, hyperlipidemia, and low

glomerular filtration rate), occupational, and environmental risk factors (Lim et al. 2012; Feigin et al. 2016).

The results from the INTERSTROKE (O'Donnell et al. 2016) study, as well as Global Burden of Disease Study (GBD) (Feigin et al. 2016) conducted in 188 countries, suggested that with achieving control of behavioral and metabolic risk factors could avert more than three-quarters of the global stroke burden. GBD additionally underlined the importance of reduction of behavioral stroke risks like a main priority in the high income countries (Feigin et al. 2016).

Clinical as well as experimental data indicate on the stroke sexually dimorphic incidence through lifetime; therefore, this gender difference, even not fully revealed, might be quite significant to better shape personalized risk and treatment. Females are protected from stroke with respect to males, due to the positive effect of ovarian hormone exposures (McCullough and Hurn 2003), but the longer life expectancy together with a poorer recovery, higher morbidity, and mortality once a stroke occurs is changing the direction of this paradigm (Glader et al. 2003).

Although there is an increasing evidence of this sex-specific differences in stroke symptoms, diagnosis, incidence, and treatment (Di Carlo et al. 2003; Glader et al. 2003; Jamc et al. 2007), controversies still exists regarding stroke epidemiology in terms of lifestyle, and metabolic risk factors between males and females (Haast et al. 2012; Poorthuis et al. 2017), making this an area worthy of further investigation.

Since knowledge about this contribution is crucial for stroke prevention strategies with well-established country and region-specific policies, we analyzed the data of the EPICOR study, the cardiovascular branch of the Italian European Investigation into Cancer and Nutrition cohort (EPIC), to estimate the difference of these preventable risk factors, their stroke impact in male and females, and the proportion of the cases that could be prevented.

Methods

EPICOR is a prospective collaborative investigation of the causes of cardiovascular diseases, performed on Italian healthy adult volunteers recruited from 1993 to 1998 as part of the EPIC study. Within the EPIC-Italy study, a total of 47,749 volunteers aged 35–74 were recruited from five centers (Varese and Turin in Northern Italy; Florence in Central Italy; and Ragusa and Naples in the South) (Palli et al. 2003). After excluding subjects with missing information on diet, anthropometry or lifestyle questionnaires ($n = 2386$), as well as prevalent cases with cardiovascular and cerebrovascular diseases ($n = 1387$), 43,976 participants were included in the present analyses (13,315 males; 30,661 females). We used the same procedures [International Classification of Diseases (ICD) 9th and 10th, and perusal of clinical records] to assess the prevalent cases as the incident cases. All participants gave written consent, and the study was approved by the local ethics committees in the participating countries and the ethical review board of the International Agency for Research on Cancer (IARC).

In EPICOR, subjects were followed up since enrolment to stroke diagnosis, death, emigration out of the region, or until the end of the follow-up period. The date of the end of follow-up varied by center, because hospital discharge file availability for updating varied as follows: December 31, 2003, for Florence; December 31, 2006, for Varese and Naples; December 31, 2007 for Ragusa; and December 31, 2008, for Turin.

Stroke identification

Record linkage between the EPICOR database and regional mortality and hospital discharge databases was performed, followed by quality control of the EPICOR database. Cardiovascular prevalent cases were excluded according to the results of the linkage with hospital discharge diagnosis archives, after confirmation of the disease by direct evaluation of medical notes, or through information derived from the baseline questionnaire, including direct questions on preexisting cardiovascular events (coronary and cerebrovascular). Suspected cerebrovascular deaths (CBVD) were identified in mortality files when ICD 10th codes: I60–I69 [cerebrovascular diseases] were reported as an underlying cause of death or when codes: I10–I15 [essential and secondary hypertension and hypertensive chronic diseases]; I46 [cardiac arrest]; I49 [cardiac arrhythmias]; and I70 [atherosclerosis] were reported as an underlying cause in association with I60–I69 as a non-principal cause of death. Fatal CBVD was assigned after verification against hospital discharge and clinical records. Persons with suspected CBVD were identified in hospital discharge forms through the ICD 9th codes: 342 [hemiplegia and hemiparesis]; 430–434 [subarachnoid, intracerebral, and unspecified intracranial hemorrhage, occlusion and stenosis of precerebral arteries, and occlusion of cerebral arteries] or 436–438 [acute and chronic cerebrovascular diseases and late effect from cerebrovascular diseases]. Cross checks with mortality data were then performed (a case was defined as nonfatal if the participant was still alive 28 days after the diagnosis). Clinical records were always retrieved to verify and confirm CBVD, using MONICA cerebrovascular criteria for diagnosis (Asplund et al. 1988). Haemorrhagic stroke was distinguished from ischemic using information on brain infarction mentioned in the

diagnosis and/or confirmed on the imaging exams (CT or MRI).

Exposure variables

A validated lifestyle questionnaire (Palli et al. 2003) was completed by each participant; it was designed to obtain detailed information on reproductive history, alcohol consumption, smoking habit, medical history, physical activity, and other lifestyle factors. This information was collated in a central database after checking, coding, and quality control procedures. We selected etiological risk factors for stroke from the Guidelines for the Primary Prevention of Stroke from the American Heart Association/American Stroke Association (Goldstein et al. 2011) on the data that were available.

Weight and height were measured at enrolment according to the EPIC protocol, with participants in light clothing and shoes removed. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Body mass index (BMI) measured at baseline was categorized (according to the WHO classification) as normal (BMI <25 kg/m^2), overweight (25–30 kg/m^2), or obese (>30 kg/m^2).

Detailed information about smoking status (never, former, and current), lifetime number of cigarettes, and duration of cigarette smoking was collected. Then, we categorized current smokers into four categories according to their current answer on smoking habit as: light (1–8 cigarettes/day), moderate (9–18 cigarettes/day), heavy (19–28 cigarettes/day), and very heavy ($\geq$29 cigarettes/day).

We assessed physical activity (PA) by a specific section of the lifestyle questionnaire and we classified it according to the Combined Total Physical Activity Index (using cut-points determined in the EPIC center of Cambridge in a heart rate monitoring validation study) (Wareham et al. 2003) that categorizes the population into four activity levels (inactive, moderately inactive, moderately active, and active) based on a cross tabulation of four categories of PA at work (sedentary, standing, manual, and heavy manual) with four categories of cycling and sport activities.

The intake of alcoholic beverages at baseline was calculated from the EPIC dietary questionnaires that have been previously validated for alcohol consumption (Kaaks et al. 1997). Participants reported the number of the standard glasses of beer, wine, and distilled spirits consumed per day or week during 12 months before recruitment. Alcohol intake was calculated as the product of mean glass volume by alcohol content of each type of alcoholic beverage. Alcohol consumption was then categorized as follows: 0 g/day (non-consumers), 1 glass/day (light drinking), 2–4 glasses/day (moderate drinkers), and >4 glasses/day (heavy drinkers).

Blood pressure was measured at recruitment visit using standardized procedures. Hypertension was defined as systolic blood pressure $\geq$140 mm Hg or diastolic blood pressure $\geq$90 mm Hg (Rose 1965). Persons on antihypertensive medication were also considered hypertensive.

We developed the Italian Mediterranean index (IMI) reflecting the Italian eating behavior. This score is based on intake of 11 items: high intakes of 6 typical Mediterranean foods (pasta; typical Mediterranean vegetables such as raw tomatoes, leafy vegetables, onion, and garlic, salad, and fruiting vegetables; fruit; legumes; olive oil; and fish); low intakes of 4 non-Mediterranean foods (soft drinks, butter, red meat, and potatoes); and also alcohol. If consumption of typical Mediterranean foods was in the third tertile of the distribution, the person received 1 point; all other intakes received 0 points. If consumption of non-Mediterranean foods was in the first tertile of the distribution, the person received 1 point. Ethanol received 1 point for intake up to 12 g day^{-1}; abstainers and persons who consumed >12 g day^{-1} received a 0. Possible scores ranged from 0 to 11(Agnoli et al. 2011). The components and standard portions are summarized in Supplementary Table 1.

Participants reporting a history (ICD 10th E10–E14 [type 1 and type 2 diabetes mellitus]), or treatment of diabetes mellitus and hyperlipidemia at baseline were considered to be diabetic or hyperlipidemic, respectively.

Statistical analysis

Baseline characteristics for categorical variables were presented as counts (percentage) and the continuous as medians and interquartile ranges. To evaluate the differences between patients with and without stroke in the prevalence of the predefined risk factors by gender, Pearson's Chi-square test was used for categorical variables, and due to non-normality of the distributions, the non-parametric Wilcoxon rank sum test was used for continuous variables.

Multivariate Cox proportional hazard models were used to assess the association of different risk factors with stroke. Hazard Ratios (HRs) and 95% Confidence Intervals (CI) were calculated. Two models are presented: a 'crude' model, stratified by center and adjusted only for age (with age categorized as $\geq$35 years every 10 years until $\leq$75 years) and an 'adjusted model', stratified by center and controlled for age and all the other risk factors presented hypertension, Body Mass Index (BMI), smoking status, hyperlipidemia, diabetes mellitus, alcohol intake, physical activity, and Italian Mediterranean index (second tertile/first tertile and third tertile/first tertile). The level of education [primary school or none (low educational level)

vocational or other secondary school (middle educational level), and university or vocational postsecondary school (high educational level)] was considered as a proxy for socioeconomic status and included in the 'adjusted model' like a possible confounding factor.

As reported in current literature, in which is stated that at light alcohol (Reynolds et al. 2003), consumption is observed lower risk for cardiovascular and cerebrovascular diseases, and the class of drinking until 1 glass per day was considered as the referent category. With regard to smoking, we computed two HRs using as the referent categories "never smoker" and "current smoker" to calculate the PAF and preventive fraction, respectively.

The Schoenfeld Residuals test was used to assess the proportional hazard assumption. To test for interactions between the predefined stroke risk factors and gender, we used a likelihood ratio test that compared the model that included the product term and the model that was without interaction. Statistical analyses were carried out for all types of stroke and separately for ischemic and hemorrhagic stroke for males and females.

We then calculated population-attributable fractions [PAFs] and 95% CI for each risk factor based on the method by Greenland and Drescher (1993) using the "punafcc post-estimation command" in STATA 13.1 (Newson 2013, 2015). These PAFs were derived from the 'adjusted' Cox proportional hazard models with baseline hazard function. PAF was, therefore, calculated to assess the proportion of strokes that could have been avoided by eliminating the following risk factors: hypertension (all hypertensive individuals are treated and become normotensive), high BMI (alternative version of all being normal/overweight), smoking (hypothetic scenario in which the individuals are never smokers), hyperlipidemia (if the individuals with hyperlipidemic risk profile would be treated to normalize their lipid levels), physical activity (if the non-active became active), diabetes (all individuals are controlling their glucose level), and alcohol use (all individuals were drinking until 1 glass/day). For the smoking category current/former and for the Italian Mediterranean Index, a preventive fraction (first/third tertile) was calculated with its 95% confidence interval (Aschengrau and Seage 2014; Hildebrandt et al. 2006).

Heterogeneity among computed PAFs and gender was assessed using the I-squared measure.

PAFs, separately or in a combination, were not computed if the corresponding risk factors were not associated statistically significantly with the outcome in the adjusted regression model.

Then, we also calculated attributable and impact fractions, derived again from fully adjusted Cox proportional hazard models (Newson 2012, 2015).

All analyses were performed with the STATA software (version 13.1; Stata Corp) and statistical significance was defined as two-tailed p value below 0.05.

Results

The study cohort comprised 43,976 participants. The median age at start of the follow-up was 50 years with interquartile range 44–56 years.

During the 478,911.6 person-years at risk (mean follow-up: 10.88 years, standard deviation: 2.46 years), 386 strokes occurred (incidence rate ratio 81 in 100,000 p-y), including 218 ischemic and 86 hemorrhagic strokes, 44 carotid revascularizations, 34 death certificates only (DCO), and 4 unspecified types of stroke.

The baseline characteristics of the cohort and stroke cases are shown in Tables 1 and 2 for males and females separately. Some behavior patterns differ substantially among the stroke cases, underlining that females tend to be more physically inactive and diabetic, while males to drink and smoke more. Except for physical activity and alcohol in females, the prevalence of the remaining risk factors was significantly associated with stroke.

In Table 3, hazard ratios of risk factors for any stroke type (males and females) are shown. Females had higher HR for hypertension [1.94 (95% CI 1.47–2.58) compared to males 1.58 (95% CI 1.13–2.19)], and diabetes [3.02 (95% CI 1.70–5.38) vs. 1.75 (95% CI 0.81–3.77)]. Examining the physical activity index, the HRs were more in favor of males, beside the wide confidence intervals, through different levels of physical activity [moderately active males 0.85 (95% CI 0.53–1.38) females 1.65 (95% CI 0.85–3.21), moderately inactive males 0.89 (95% CI 0.58–1.35) females 1.30 (95% CI 0.71–2.38)]. The third tertile of the Italian Mediterranean Index was inversely associated with risk of all types of stroke [males 0.50 (95% CI 0.37–0.67); females 0.46 (95% CI 0.30–0.74)]. The HR for the hazard stroke morbidity for alcohol among males resulted in a typical J-shaped curve [non-consumers 1.11 (95% CI 0.61–2.00), 2–4 glasses/day 1.36 (95% CI 0.88–2.11), and >4 glasses/day 2.39 (95% CI 1.44–3.96)]. Among the abstainers, a higher risk was noted compared to the reference category [males 1.11 (95% CI 0.61–2.00) females 1.41 (95% CI 1.03–1.93)].

There was no statistical significant interaction between the studied etiological risk factors and gender at $\alpha = 0.05$.

In Table 4, are presented population-attributable fraction and their combination if the corresponding risk factors were associated significantly in the previously computed fully adjusted Cox model. Among males, the biggest burden for all stroke types, with a PAF of 17% (95% CI 4–28%), was provided by smoking, followed by

Table 1 Baseline individual characteristics in stroke cases according to type in males' European prospective investigation into cancer and nutrition (EPIC), 1993/8-2008, Italy

	Cohort (*N*, %)	All types of stroke (*N*, %)	*p*	Ischemic (*N*, %)	Hemorrhagic (*N*, %)
n.	13,315	157		99	26
Age (median, IQR)	50 (44–56)	56 (50–60)	<0.001	57 (50–59)	56.5 (47–61)
Hypertension			<0.001		
No	10,137 (76.1)	95 (60.5)		59 (59.6)	13 (50.0)
Yes	3178 (23.9)	62 (39.5)		40 (40.4)	13 (50.0)
BMI			0.044		
<25	4540 (34.1)	43 (27.4)		27 (27.3)	6 (23.1)
≥25 < 30	6804 (51.1)	81 (51.6)		51 (51.5)	13 (50.0)
≥30	1971 (14.8)	33 (21.0)		21 (21.2)	7 (26.9)
Smoking			0.008		
Never	4028 (30.2)	39 (24.8)		20 (20.2)	13 (50.0)
Former	5579 (41.9)	57 (36.3)		39 (39.4)	6 (23.1)
Current	3708 (27.9)	61 (38.9)		40 (40.4)	7 (26.9)
Hyperlipidemia			0.008		
No	9184 (68.9)	93 (59.2)		61 (61.6)	17 (65.4)
Yes	4131 (31.1)	64 (40.8)		38 (38.4)	9 (34.6)
Diabetes mellitus			0.007		
No	13,088 (98.3)	150 (95.5)		95 (96.0)	25 (96.2)
Yes	227 (1.7)	7 (4.5)		4 (4.0)	1 (3.8)
Physical activity			0.023		
Active	3667 (27.5)	40 (25.5)		29 (29.3)	7 (26.9)
Moderately active	3160 (23.7)	30 (19.1)		17 (17.2)	4 (15.4)
Moderately inactive	4752 (35.7)	54 (34.4)		34 (34.3)	10 (38.7)
Inactive	1736 (13.1)	33 (21.0)		19 (19.2)	5 (19.0)
Italian Mediterranean index			<0.001		
First tertile	4.211 (31.6)	52 (33.1)		34 (34.3)	7 (26.9)
Second tertile	5520 (41.5)	69 (43.0)		46 (46.5)	8 (30.8)
Third tertile	3548 (28.9)	36 (22.9)		19 (19.2)	11(42.3)
Alcohol			<0.001		
Non-consumers	1935 (14.5)	19 (12.1)		10 (10.1)	6 (23.1)
1 glass/day	3869 (29.1)	29 (18.5)		21 (21.2)	3 (11.5)
2–4 glasses/day	6024 (45.2)	72 (45.9)		42 (42.4)	14 (53.9)
>4 glasses/day	1487 (11.2)	37 (23.5)		26 (26.3)	3 (11.5)
Center			<0.001		
Florence	3211 (24.1)	38 (24.2)		23 (23.2)	4 (15.5)
Varese	2141 (16.1)	48 (30.6)		24 (24.2)	12 (46.1)
Torino	5277 (39.6)	47 (29.9)		36 (36.4)	7 (26.9)
Ragusa and Naples	2686 (20.2)	24 (15.3)		16 (16.2)	3 (11.5)

IQR interquartile ranges, *BMI* body mass index <25 kg/m^2 normal; 25–30 kg/m^2 overweight; >30 kg/m^2 obese

* *p* values from Chi-square test for categorical variables and Wilcoxon rank sum for continuous variable

alcohol consumption [PAF 14% (95% CI 5–22%)] and hypertension with 13% (95% CI 2–25%). The total proportion of strokes that could be attributed to the combination of the following risk factors: hypertension, current smoking, hyperlipidemia, and consumption of >4 glasses/day was 46% (95% CI 32–58%). Regarding the females, hypertension [PAF 18% (95% CI 9–26%)], smoking [15% (95% CI 7–22%)], and alcohol abstinence [14% (95% CI 1–26%)] were taking the major part of the stroke burden. Here, the combination of PAF accounted for 48% (95% CI 35–59%). The test for heterogeneity for the PAF of alcohol consumption, as

Table 2 Baseline individual characteristics in stroke cases according to type in females' European prospective investigation into cancer and nutrition (EPIC), 1993/8-2008, Italy

	Cohort (*N*, %)	All types of stroke (*N*, %)	*p**	Ischemic (*N*, %)	Hemorrhagic (*N*, %)
n.	30,661	229		119	60
Age (median, IQR[I])	50 (44–56)	57 (52–62)	<0.001	57 (53–63)	56 (50.5–59.5)
Hypertension			<0.001		
No	24,904 (81.2)	142 (62.0)		73 (61.3)	36 (60.0)
Yes	5757 (18.8)	87 (38.0)		46 (38.7)	24 (40.0)
BMI[b]			0.041		
<25	15,224 (49.7)	95 (41.5)		42 (35.2)	30 (50.0)
≥25 < 30	10,776 (35.2)	96 (41.9)		51 (42.9)	24 (40.0)
≥30	4661 (15.1)	38 (16.6)		26 (21.9)	6 (10.0)
Smoking			0.036		
Never	16,475 (53.7)	126 (55.0)		72 (60.5)	32 (53.3)
Former	6191 (20.2)	32 (14.0)		16 (13.5)	10 (16.7)
Current	7995 (26.1)	71 (31.0)		31 (26.0)	18 (30.0)
Hyperlipidemia			<0.001		
No	24,393 (79.6)	152 (66.4)		78 (65.5)	46 (76.7)
Yes	6268 (20.4)	77 (33.6)		41 (34.5)	14 (23.3)
Diabetes mellitus			<0.001		
No	30,217 (98.6)	216 (94.3)		110 (92.4)	58 (96.7)
Yes	444 (1.4)	13 (5.7)		9 (7.6)	2 (3.3)
Physical activity			0.075		
Active	2902 (9.5)	12 (5.3)		3 (2.5)	7 (11.7)
Moderately active	4601 (15.0)	32 (13.9)		22 (18.5)	7 (11.7)
Moderately inactive	12,030 (39.2)	88 (38.4)		46 (38.7)	22 (36.6)
Inactive	11,128 (36.3)	97 (42.4)		48 (40.3)	24 (40.0)
Italian Mediterranean index			<0.001		
First tertile	8848 (29.2)	70 (30.6)		36 (30.3)	19 (31.7)
Second tertile	12,669 (41.2)	93 (40.6)		51 (42.9)	23 (38.3)
Third tertile	9084 (29.6)	66 (28.8)		32 (26.8)	18 (30.0)
Alcohol			0.077		
Non-consumers	13,554 (44.2)	114 (49.8)		62 (51.1)	28 (46.7)
1 glass/day	10,930 (35.7)	63 (27.5)		31 (26.0)	20 (33.3)
2–4 glasses/day	5864 (19.1)	50 (21.8)		24 (21.2)	12 (20.0)
>4 glasses/day	313 (1.0)	2 (0.9)		2 (1.7)	–
Center			<0.001		
Florence	9705 (31.7)	47 (20.5)		29 (24.4)	12 (20.0)
Varese	8942 (29.2)	114 (49.8)		58 (48.7)	26 (43.3)
Torino	4163 (13.5)	33 (14.4)		12 (10.1)	15 (25.0)
Ragusa and Naples	7851 (25.6)	35 (15.3)		20 (16.8)	7 (11.7)

IQR interquartile ranges, *BMI* body mass index <25 kg/m^2 normal; 25–30 kg/m^2 overweight; >30 kg/m^2 obese

* *p* values from Chi-square test for categorical variables and Wilcoxon rank sum for continuous variable

well as the preventive fraction for smoking and gender was statistically significant at $\alpha = 0.05$.

Furthermore, attributable fractions among the exposed and impact fractions were computed. Among males consumers of alcohol beverages, the impact fractions for heavy drinking males contrasted with a hypothetical scenario of consuming 2–4 drinks per day was 43% (95% CI 15–62%), of drinking only one glass per day 58% (95% CI 32–74%), and of not drinking at all 54% (95% CI 18–74%). In females, because of small numbers, it was not possible assessing the impact fraction for alcohol consumption (Table 4).

Table 3 Hazard ratios and 95% CI for any stroke type in relation to preventable risk factors, European prospective investigation into cancer and nutrition (EPIC), 1993/8-2008, Italy

	Males		Females	
	Hazard ratio (95% CI) crude*	Hazard ratio (95% CI) adj.**	Hazard Ratio (95% CI) crude*	Hazard ratio (95% CI) adj.**
Hypertension				
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	1.65 (1.19–2.29)	1.58 (1.13–2.19)	1.86 (1.42–2.44)	1.94 (1.47–2.58)
BMI				
<25	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
≥25 <30	1.16 (0.80–1.68)	1.02 (0.70–1.49)	1.15 (0.86–1.52)	1.03 (0.77–1.38)
≥30	1.64 (1.04–2.60)	1.23 (0.76–1.98)	1.05 (0.72–1.54)	0.78 (0.52–1.17)
Smoking				
Never	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Former	0.99 (0.66–1.49)	0.92 (0.61–1.39)	0.97 (0.66–1.44)	1.03 (0.69–1.53)
Current	1.99 (1.33–2.98)	1.80 (1.19–2.72)	1.84 (1.36–2.48)	1.96 (1.44–2.66)
Current	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Former	0.50 (0.35–0.72)	0.51 (0.35–0.74)	0.53 (0.35–0.80)	0.53 (0.34–0.80)
Hyperlipidemia				
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	1.52 (1.10–2.09)	1.46 (1.06–2.04)	1.41 (1.07–1.88)	1.38 (1.04–1.83)
Diabetes mellitus				
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	1.92 (0.90–4.11)	1.75 (0.81–3.77)	3.21 (1.83–5.66)	3.02 (1.70–5.38)
Physical activity				
Active	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Moderately active	0.83 (0.52–1.33)	0.85 (0.53–1.38)	1.66 (0.86–3.23)	1.65 (0.85–3.21)
Moderately inactive	0.87 (0.58–1.31)	0.89 (0.58–1.35)	1.35 (0.74–2.47)	1.30 (0.71–2.38)
Inactive	1.30 (0.81–2.08)	1.20 (0.74–1.94)	1.83 (1.00–3.38)	1.65 (0.89–3.04)
Italian Mediterranean index				
First tertile	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Second tertile	0.78 (0.62–0.98)	0.88 (0.73–1.08)	0.93 (0.88–1.02)	1.00 (0.97–1.05)
Third tertile	0.69 (0.57–0.97)	0.50 (0.37–0.67)	0.54 (0.34–0.80)	0.46 (0.30–0.74)
Alcohol				
1 glass/day	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Non-consumers	1.22 (0.68–2.17)	1.11 (0.61–2.00)	1.49 (1.09–2.02)	1.41 (1.03–1.93)
2–4 glasses/day	1.37 (0.89–2.12)	1.36 (0.88–2.11)	1.43 (0.99–2.08)	1.37 (0.94–1.99)
>4 glasses/day	2.69 (1.64–4.42)	2.39 (1.44–3.96)	1.46 (0.36–5.98)	1.29 (0.31–5.30)

BMI body mass index <25 kg/m^2 normal; 25–30 kg/m^2 overweight; >30 kg/m^2 obese

* HRs derived from Cox proportional hazards model stratified by center and adjusted for age ** HRs derived from multivariate Cox proportional hazards model stratified by center and adjusted for age and all other risk factors presented (hypertension, BMI, smoking, hyperlipidemia, diabetes, physical activity, Italian Mediterranean index, alcohol consumption, and level of education)

Restricting the analyses to ischemic stroke in females, hypertension was taking the biggest burden, with 17% (95% CI 4–29%), for a total PAF of 46% (95% CI 26–61%). In males, smoking had the highest PAF, with 22% (95% CI 7–35%), while the total PAF was 48% (95% CI 29–62%) (Supplementary Table 2). Due to the limited number of stroke events, we were unable to separately analyze the risk factors and their corresponding PAF for hemorrhagic stroke.

When we divided the smoking category into four subcategories, females fell mostly in the light (prevalence 9.9%) and medium (prevalence 9.3%) smoking category, while the males where medium (prevalence 9.1%) and heavy (prevalence 8.6%) smokers (Table 5). Contrasting a smoking

Table 4 Population-attributable fraction (PAF), impact fraction (IF), and attributable fraction (AF) of etiological risk factors for any stroke type by gender, European prospective investigation into cancer and nutrition (EPIC), 1993/8-2008, Italy

Etiological factor	Stratum	Males			Females		
		Prev. (%)	PAF* (95% CI)	IF or AF* (95% CI)	Prev. (%)	PAF (95% CI)	IF or AF (95% CI)
Hypertension	Yes	23.9	13% (2–25%)	37% (11–55%)	18.8	18% (9–26%)	48% (31–62%)
BMI	1. <25 (ref.)	34.1	n.a.	n.a.	49.7	n.a.	n.a.
	2. ≥25 < 30	51.1			35.2		
	3. ≥30	14.8			15.1		
Smoking	1. Never (ref.)	30.2		44% (16–63%)	53.7		
	2. Former	41.9			20.2		
	3. Current	27.9	17% (4–28%)		26.1	15% (7–22%)	49% (30–62%)
		Preventive fraction			Preventive fraction		
	Current (ref.)	27.9			26.1		
	Former	41.9	21% (15–27%)		20.2	9% (1–17%)	
Hyperlipidemia	Yes	31.1	13% (1–24%)	32% (5–51%)	20.4	9% (1–18%)	27% (3–46%)
Diabetes mellitus	Yes	1.7	n.a.	n.a.	1.4	4% (1–7%)	67% (41–81%)
Physical activity	1. Active (ref.)	27.5	n.a.	n.a.	9.5	n.a.	n.a.
	2. Moderately active	23.7			15.0		
	3. Moderately inactive	35.7			39.2		
	4. inactive	13.1			36.3		
Italian	1. First tertile (ref.)	31.6			29.2		
Mediterranean	2. Second tertile	41.5	Preventive fraction		41.2	Preventive fraction	
Index (IMI)	3. Third tertile	28.9	15% (10–20%)		29.6	16% (12–20%)	
Alcohol	1. 1 glass/day (ref.)	29.1	n.a.	(4–1) 58% (32–74%)	35.7	14% (1–26%) (2–1)	(2–1) 29% (3–48%)
	2. Non-consumers	14.5	n.a.	(4–2) 54% (18–74%)	44.2	n.a.	
	3. 2–4 glasses/day	45.2		(4–3) 43% (15–62%)	19.1	n.a.	
	4. >4 glasses/day	11.2	14% (5–22%)(4–1)		1.0		
Combination[a]		46% (32–58%)			48% (35–59%)		

* PAF, IF, and AF (attributable/impact fraction among exposed) are derived from the 'adjusted' Cox models. PAF Smoking: if the current smokers were never smokers. PF: if the current smokers became former smokers; third/first tertile of IMI. PAF Alcohol (2–1): if the non-consumers were drinking 1 glass/day; (4–1): if the consumers of >4 glasses/day were drinking 1 glass/day. AF (4–1) of a consumer of >4 glasses/day drinking 1 glass/day; (4–2) of a consumer of >4 glasses/day becoming non-consumer. IF (4-3) of a consumer of >4 glasses/day drinking 2–4 glasses/day; AF (2-1): if the non-consumers were drinking 1 glass/day

[a] Combination (hypertension, current smokers, and hyperlipidemia if the consumers of >4 glasses/day were drinking 1 glass/day) for males; [a](hypertension, current smokers, and hyperlipidemia, diabetes if the non-consumers were drinking 1 glass/day) for females

BMI body mass index, Prev—prevalence, ref—reference category, *na* not applicable

subcategory with a presumed scenario of different smoking decrease resulted in an impact fraction that among males was highest for switching from the very heavy smoking category to that of light smoking, while for females, the change from the heavy to the light smoking category had the strongest impact [IF males very heavy/light 72% (95% CI 27–89%) females heavy/light 60% (95% CI 25–79%)].

Discussion

We found that about half of all strokes that occurred in our cohort were attributable to established modifiable (or virtually modifiable) etiological factors and could theoretically be prevented by eliminating them in a gender-specific target population.

Table 5 Impact fraction (IF), attributable fraction (AF) with 95% CI of a different smoking category for any stroke type by gender, European prospective investigation into cancer and nutrition (EPIC), 1993/8-2008, Italy

Smoking category	Prevalence (%)	Hazard ratio (95% CI) (adj.)[a]	Attributable fraction (AF) Starting point of the exposure category			
			Very heavy	Heavy	Medium	Light
Destination point of the reference category						
Never						
Males	30.2	1 (ref.)	69% (36–85%)	63% (39–78%)	31% (0–61%)	0% (0–49%)
Females	53.7	1 (ref.)	52% (0–85%)	68% (49–80%)	54% (29–70%)	19% (0–51%)
Former						
Males	41.9	0.92 (0.61–1.39)	71% (42–86%)	66% (45–79%)	36% (0–64%)	0% (0–51%)
Females	20.2	1.03 (0.69–1.53)	50% (0–85%)	67% (43–81%)	52% (20–72%)	16% (0–53%)

Smoking category	Prevalence (%)	Hazard ratio (95% CI) (adj.)[a]	Impact fraction (IF) Starting point of the exposure category		
Destination point of the reference category					
Light (1–8 cig/day					
Males	7.4	0.91 (0.43–1.97)	72% (27–89%)	67% (26–85%)	37% (0–73%)
Females	9.9	1.24 (0.75–2.05)	41% (0–83%)	60% (25–79%)	43% (0–69%)
Medium (9–18 cig/day)					
Males	9.1	1.46 (0.82–2.59)	55% (0–80%)	47% (0–71%)	
Females	9.3	2.18 (1.41–3.37)	0% (0–68%)	30% (0–60%)	
Heavy (19–28 cig/day)					
Males	8.6	2.74 (1.62–4.62)	15% (0–59%)		
Females	5.6	3.12 (1.98–4.93)	0% (0–55%)		
Very heavy (≥29 cig/day)					
Males	2.8	3.21 (1.55–6.66)			
Females	1.3	2.09 (0.65–6.63)			

[a] HRs derived from multivariate Cox proportional hazard models stratified by center and adjusted for age, hypertension, BMI, smoking, hyperlipidemia, diabetes, physical activity, Italian Mediterranean Index, alcohol consumption and education. Impact fraction (IF) is a proportion of disease burden among exposed arising from comparison of incidences of an observed exposure pattern with a counterfactual one in which the exposure is only partially removed, for example. The IF of a very heavy smoker (observed exposition pattern) compared to heavy smoker (counterfactual reference category of a partial exposure removal) is 15% (95% CI 0–59%)

In the present article, to translate the results from analytic epidemiology to public health practice, we used the concepts of population-attributable risk percent or population-attributable fraction (PAF), defined as the percent reduction in incidence that would be achieved if the population with its current exposure pattern, had become entirely unexposed (Rothman et al. 2008) and that of preventive fraction (PF), which estimates finding utilization when an exposure seems to reduce the risk and gives the percentage of cases that can be prevented if they are exposed to the presumed protective factor in contrast to the unexposed (Aschengrau and Seage 2014). We also derived the attributable fraction (AF) among exposed, a measure that does not take the prevalence of the exposure into account as the PAF and PF yet quantifies the proportion of the disease burden among diseased people that is caused by the exposure (Rothman 2012). As more pragmatic use of the concept of this attributable fraction, arising from the fact that complete removal of an exposure is often very unrealistic, we used a measure, the impact fraction (IF), which is a comparison of incidences in the observed exposure pattern with a counterfactual one in which the exposure is only partially removed (Rothman et al. 2008).

The baseline characteristics of the EPIC participants met similarities with a recent meta-analysis on the gender gap in stroke that showed that females were globally older, less likely to smoke cigarettes, drink alcohol, or present hyperlipidemia, nevertheless more hypertensive than males (Giralt et al. 2012).

There are several proposed mechanisms for the development of hypertension that are unique to females deriving from the falling estrogen levels during the menopause, yet not omitting pre-eclampsia, oral contraceptives, and polycystic ovary syndrome for the beginning and progression of hypertension at younger age (Abramson and Melvin 2014). These possible mechanisms may perhaps explain the higher risk of stroke among hypertensive females, as well as the expected higher PAF for any stroke type among them (PAF males 13%, 95% CI 2–25%, females 18%, 95% CI 9–26%).

Obesity among the males in EPICOR cohort was a risk factor for stroke, even if the result was not statistically significant. Females did not follow the expected trend. The INTERSTROKE study, a large case–control study aimed at ascertaining risk factors for stroke, indicated that BMI was not associated with stroke while revealing and pointing at the possible role of the waist-to-hip ratio on the increased stroke risk (O'Donnell et al. 2010).

A higher risk of stroke in diabetic females than in males was clearly confirmed by a recent meta-analysis of 64 cohorts [pooled adjusted RR females 2.28 (95% CI 1.93–2.69) males 1.83 (95% CI 1.60–2.08)] (Peters et al. 2014). It has been hypothesized a female's greater insulin sensitivity at sites associated with insulin resistance, namely, the liver and the skeletal muscle, (Geer and Shen 2009) supporting the idea that the metabolic and vascular risk factor profile of females has to deteriorate to a greater extent than that of males before the onset of manifest diabetes mellitus (Wannamethee et al. 2012).

A meta-analysis on the association between physical activity (PA) and stroke outcomes in males and females indicated that higher levels of PA may be required among females to achieve a significant risk reduction as in males (Diep et al. 2010). The same difference across different levels of physical activity was to identify in EPICOR.

The risk of stroke morbidity associated with alcohol consumption among males resulted in a J-shaped curve, whereas among females, being abstainers (non-consumers) was associated with a higher risk than in males, in comparison with consuming until 1 drink a day. Among the recent key findings from the Nurses' Health Study, moderate alcohol intake (defined as consumption of 5–15 g/day) was associated with a lower risk for many health outcomes (hypertension, myocardial infarction, sudden cardiac death, cognitive decline, and all-cause mortality) as well as stroke, compared with abstainers and females who consumed more than 1 drink per day (Mostofsky et al. 2016). A potential mechanism to which is account this protective alcohol effect described in the literature is the increase of the plasma high-density lipoprotein cholesterol (HDL) concentration, a well-established major protective factor against cardiovascular disease (Matsumoto et al. 2014) which has been reported to be significantly higher in females than males (Musha et al. 2006).

In a systematic review and meta-analysis on alcohol consumption and the risk of morbidity and mortality for different stroke types, a protective effect up to 37 g/day (about 3 drinks/day) among males and 46 g/day (or about 4 drinks/day) among women was observed (Patra et al. 2010) relative to the lifetime abstainers. Among males, the impact fraction was highest for moving from the heavy drinking category to that of light drinking, although it was quite similar to the impact fractions computed for switching to the other categories (moderate or absteiners) and with a wide uncertainty of the estimates and their confidence intervals (Table 4), their overlapping, however, displays the message that when a complete removal of alcohol consumption is unreal, especially among the heavy drinkers, decrease of just 1 drink a day could allow them to lower their risk to the same level as of that of the moderate drinkers. The beneficial effects of quitting smoking among former smokers on stroke risk were similar among genders (f/m sex-specific relative risks ratio (RRR), 1.10 [0.99–1.22]), results published in a recent meta-analysis (Peters et al. 2013), consistently with our results. Acknowledging the similar HRs, and additionally considering the twofold prevalence of former smokers among males than females, translates in a higher preventive fraction for males.

The EPICOR study has several strengths: from them, the very accurate case finding and nearly complete follow-up (loss of potential person-years is smaller than 2.5% reducing the probability of selection bias, and low proportion of missing values of the variables were <5%), the prospective design (risk factors are detected before the onset of the disease and, therefore, are not affected by reverse causality), the large sample size, and the use of detailed information on lifestyle and anthropometric variables.

However, this relatively old data should be interpreted with caution, since during the long follow-up of almost 11 years, risk factor profiles of some participants may have changed, altering the associations we found in both directions. Furthermore, our study population, consisted of generally younger people who live in a middle or high income area, is obtaining a higher risk awareness than of that in the general population, which means that our results may not be generalizable to underprivileged,

ethnically diverse or people older than 75 years of age. In addition, we should not put aside the aspect that some risk factors may have already caused irreversible damage, especially long-lasting diabetes or to may be markers of other not modifiable factors that may not be modifiable leading to overestimation of the computed PAFs.

Conclusion

In males, smoking together with excessive alcohol consumption takes the biggest burden of stroke cases and also due to its well-documented adverse effects should remain among the priorities of any stroke prevention program.

In females, hypertension is still the main risk factor of stroke, so screening for hypertension together with prediabetes in females could have a substantial effect on the prevention of the adverse vascular events. Taking into consideration the low prevalence of smoking cessation, the preventive campaigns should be more detailed and targeted on this population.

Using this PAF measurements, we can better plan prevention campaigns and lower the premature mortality in Italy setting our strategies on well-defined gender-specific population.

Acknowledgements EPICOR is supported by Compagnia di San Paolo. The Italian EPIC collaboration is supported by the Italian Association for Cancer Research (AIRC). The founders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Compliance with ethical standards

Conflict of interest Authors have no conflicts of interest in connection with the paper.

Informed consent All participants gave written informed consent, and the study was approved by the local ethics committees in the participating countries and the ethical review board of the International Agency for Research on Cancer (IARC).

References

Abramson BL, Melvin RG (2014) Cardiovascular risk in women: focus on hypertension. Can J Cardiol 30:553–559. doi:10.1016/j.cjca.2014.02.014

Agnoli C, Krogh V, Grioni S et al (2011) A priori-defined dietary patterns are associated with reduced risk of stroke in a large italian cohort. J Nutr 141:1552–1558. doi:10.3945/jn.111.140061.In

Aschengrau A, Seage GR (2014) Essentials of epidemiology in public health, 3rd edn. Jones and Bartlett Learning, Burlington

Asplund K, Tuomilehto J, Stegmayr B et al (1988) Diagnostic criteria and quality control of the registration of stroke events in the MONICA project. Acta Med Scand Suppl 728:26–39

Di Carlo A, Lamassa M, Baldereschi M et al (2003) Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe data from a multicenter multinational hospital-based registry. Stroke 34:1114–1119. doi:10.1161/01.STR.0000068410.07397.D7

Diep L, Kwagyan J, Kurantsin-Mills J et al (2010) Association of physical activity level and stroke outcomes in men and women: a meta-analysis. J Women's Heal 19:1815–1822. doi:10.1089/jwh.2009.1708

Feigin VL, Roth GA, Naghavi M et al (2016) Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Glob Heal 4422:1–12. doi:10.1016/S1474-4422(16)30073-4

Geer EB, Shen W (2009) Gender differences in insulin resistance, body composition, and energy balance. Gend Med 6:60–75. doi:10.1016/j.genm.2009.02.002

Giralt D, Domingues-Montanari S, Mendioroz M et al (2012) The gender gap in stroke: a meta-analysis. Acta Neurol Scand 125:83–90. doi:10.1111/j.1600-0404.2011.01514.x

Glader E, Stegmayr B, Norrving B et al (2003) Sex differences in management and outcome after stroke. Stroke 34:1970–1975. doi:10.1161/01.STR.0000083534.81284.C5

Goldstein LB, Bushnell CD, Adams RJ et al (2011) Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 42:517–584. doi:10.1161/STR.0b013e3181fcb238

Greenland S, Drescher K (1993) Maximum likelihood estimation of the attributable fraction from logistic models. Biometrics 49:865–872

Haast RAM, Gustafson DR, Kiliaan AJ (2012) Sex differences in stroke. J Cereb Blood Flow Metab 32:2100–2107. doi:10.1038/jcbfm.2012.141

Hildebrandt M, Bender R, Gehrmann U, Blettner M (2006) Calculating confidence intervals for impact numbers. BMC Med Res Methodol 6:32. doi:10.1186/1471-2288-6-32

Jamc C, Pilote L, Dasgupta K et al (2007) A comprehensive view of sex-specific issues related to cardiovascular disease. Can Med Assoc J 176:S1–S44. doi:10.1503/cmaj.051455

Kaaks R, Slimani N, Riboli E (1997) Pilot phase studies on the accuracy of dietary intake measurements in the EPIC project: overall evaluation of results. Int J Epidemiol 26:26–36. doi:10.1093/ije/26.suppl_1.S26

Lim SS, Vos T, Flaxman AD et al (2012) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2224–2260. doi:10.1016/S0140-6736(12)61766-8

Lozano R, Naghavi M, Foreman K et al (2012) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2095–2128. doi:10.1016/S0140-6736(12)61728-0

Matsumoto C, Miedema MD, Ofman P et al (2014) An expanding knowledge of the mechanisms and effects of alcohol consumption on cardiovascular disease. J Cardiopulm Rehabil Prev 34:159–171. doi:10.1097/HCR.0000000000000042

McCullough LD, Hurn PD (2003) Estrogen and ischemic neuroprotection: an integrated view. Trends Endocrinol Metab 14:228–235. doi:10.1016/S1043-2760(03)00076-6

Mostofsky E, Mukamal KJ, Giovannucci EL et al (2016) Key findings on alcohol consumption and a variety of health outcomes From the Nurses' Health Study. Am J Public Heal 106:1586–1591. doi:10.2105/AJPH.2016.303336

Musha H, Hayashi A, Kida K et al (2006) Gender difference in the level of high-density lipoprotein cholesterol in elderly Japanese patients with coronary artery disease. Intern Med 45:241–245. doi:10.2169/internalmedicine.45.1528

Newson R (2012) Scenario comparisons: How much good can we do? National Heart and Lung Institute, Imperial College London 18th UK Stata Users' Group Meeting

Newson R (2013) Attributable and unattributable risks and fractions and other scenario comparisons. Stata J 13:672–698

Newson R (2015) PUNAFCC: Stata module to compute population attributable fractions for case-control and survival studies. In: Stat. Softw. Components. https://ideas.repec.org/c/boc/bocode/s457354.html. Accessed 4 May 2017

O'Donnell MJ, Xavier D, Liu L et al (2010) Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 376:112–123. doi:10.1016/S0140-6736(10)60834-3

O'Donnell MJ, Chin SL, Rangarajan S et al (2016) Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 388:761–775. doi:10.1016/S0140-6736(16)30506-2

Palli D, Berrino F, Vineis P et al (2003) A molecular epidemiology project on diet and cancer: the EPIC-Italy Prospective Study. Design and baseline characteristics of participants. Tumori 89:586–593

Patra J, Taylor B, Irving H et al (2010) Alcohol consumption and the risk of morbidity and mortality for different stroke types—a systematic review and meta-analysis. BMC Public Health 10:258. doi:10.1186/1471-2458-10-258

Peters SAE, Huxley RR, Woodward M (2013) Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. Stroke 44:2821–2829. doi:10.1161/STROKEAHA.113.002342

Peters SAE, Huxley RR, Woodward M (2014) Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. Lancet 383:1973–1980. doi:10.1016/S0140-6736(14)60040-4

Poorthuis MHF, Algra AM, Algra A et al (2017) Female- and male-specific risk factors for stroke: a systematic review and meta-analysis. JAMA Neurol 74:75–81. doi:10.1001/jamaneurol.2016.3482

Reynolds K, Lewis LB, Nolen JDL, Kinney GL (2003) Alcohol consumption and risk of stroke: a meta-analysis. JAMA 289:579–588

Rose G (1965) Standardisation of observers in blood-pressure measurement. Lancet 1:673–674. doi:10.1016/S0140-6736(65)91827-1

Rothman KJ (2012) Epidemiology : an introduction, 2nd edn. Oxford University Press, Oxford

Rothman KJ, Greenland S, Lash TL (2008) Modern epidemiology, 3rd edn. Lippincott Williams and Wilkins, Philadelphia

Wang H, Naghavi M, Allen C et al (2015) Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388:1459–1544. doi:10.1016/S0140-6736(16)31012-1

Wannamethee SG, Papacosta O, Lawlor DA et al (2012) Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Health Study. Diabetologia 55:80–87. doi:10.1007/s00125-011-2284-4

Wareham NJ, Jakes RW, Rennie KL et al (2003) Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Heal Nutr 6:407–413. doi:10.1079/PHN2002439