Association of Atrial Fibrillation and Stroke: Analysis of Maccabi Health Services Cardiovascular Database

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ABSTRACT: **Background:** Stroke is a leading cause of death and disability worldwide. The risk factors for stroke overlap those for cardiovascular disease. Atrial fibrillation (AF) is a particularly strong risk factor and is common, particularly in the elderly. Maccabi Healthcare Services (MHS) has maintained a vascular registry of clinical information for over 100,000 members, among them patients with heart disease and stroke.

Objectives: To determine the prevalence of stroke in MHS, and whether the association of AF and stroke, along with other risk factors, in the Maccabi population is similar to that in published studies.

Methods: Data on stroke and AF patients aged 45 and older were collected from the database for the year 2010, including age, previous transient ischemic attack (TIA), body mass index (BMI), prior myocardial infarction (MI), diabetes, hypertension, anticoagulation and dyslipidemia. A cross-sectional analysis was used to estimate stroke prevalence by AF status. A case-control analysis was also performed comparing a sample of stroke and non-stroke patients. This permitted estimation of the strength of associations for atrial fibrillation and various other combinations of risk factors with stroke.

Results: Stroke prevalence ranged from 3.5 (females, age 45–54 years) to 74.1 (males, age 85+) per thousand in non-AF members, and from 29 (males, age 45–54) to 165 (males, age 85+) per thousand for patients with AF. AF patients had significantly more strokes than non-AF patients in all age groups. Stroke prevalence increased with age and was significantly higher in males. Multivariable analysis revealed that male gender, increasing age, AF, hypertension, diabetes, and history of TIA were highly significant risk factors for stroke. In addition, for males, dyslipidemia and prior MI were moderately strong risk factors.

Conclusions: Analysis of the MHS vascular database yielded useful information on stroke prevalence and association of known risk factors with stroke, which is consistent with the epidemiological literature elsewhere. Further analysis of health fund data could potentially provide useful information in the future.

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KEY WORDS: atrial fibrillation (AF), stroke, vascular registry, stroke risk factors, health maintenance organization

Stroke is the leading cause of disability worldwide, with a high cost in terms of quality of life, lost function, and suffering [1]. It is the third leading cause of death [2]. There are about 61,000 stroke survivors in Israel [3] and an estimated 13,000 new strokes a year [4]. About 50% of stroke survivors are left with functional disability, resulting in loss of productivity, poor quality of life, and burden on families and the health care system [5]. However, the mortality from stroke has fallen significantly in recent years, as has the incidence of primary [6] and secondary [7] strokes. The incidence of stroke increases significantly with age and is higher for men. While the annual incidence of stroke is around 1 per thousand in men aged ≤ 45, the risk increases tenfold by the sixth decade and 100-fold by age 80 [6]. The prevalence of stroke with atrial fibrillation (AF) in the aforementioned study cohorts varies widely, ranging from 8% to 25%. While incidence data may better reflect risk factors, prevalence may be a better indicator than incidence for disease burden at the population level [8].

The main risk factors for stroke are similar to those for ischemic heart disease [9]. The leading modifiable risk factor for both ischemic and hemorrhagic strokes is hypertension. Hypertension results in an estimated two- to sevenfold increased risk of stroke, particularly the hemorrhagic type, and thus significant effort is expended in prevention [10].

Dyslipidemia is another modifiable risk factor for stroke. As in cardiovascular disease, the pathogenesis of atheromatous plaques in large and small arteries in the brain results in inflammation, occlusion and ischemia. Lipid-lowering drugs, particularly statins, are effective for primary and secondary prevention [11]. Other potentially modifiable factors include smoking, diabetes, diet, hypercoagulation states and cardiac disease, particularly AF [12].

Atrial fibrillation is extremely common in the elderly population, with a prevalence of up to 17% among those 80 and older [13]. The incidence of new or recurrent stroke in AF patients ranges from 1.5% to 10% per year, depending on the presence of other risk factors. The two main types of AF, chronic and paroxysmal, have both been associated with increased risk. Treatment with vitamin K antagonists, such as warfarin, reduces the risk by more than half and improves post-stroke outcomes

[14]. However, treatment with warfarin is not without danger and requires close monitoring. When anticoagulation is properly monitored the incidence of major bleeding is < 1.5% and intracranial hemorrhage is 0.4%. Consequently, several clinical rules have been developed to determine for which patients the benefit outweighs the risks [15]. Patients considered at lower risk for stroke may be treated with aspirin. Previously, the most common algorithm to assess risk was the CHADS2 method [16]. This consists of adding up points for the following: history of congestive heart failure (CHF), hypertension, age over 75, diabetes, and previous cerebrovascular event. The sum is then used to stratify patients into low (< 1%), medium (< 2.5%) and high (> 4%) risk. Recently, the CHADS2-VASc scale, a refinement of the CHADS2, has been studied and widely adopted as a more sensitive alternative to properly classify low risk patients [17,18]. This score incorporates female gender, age over 65, and a history of previous vascular disease as additional risk factors.

Since 2001, as required by the Israel Ministry of Health, all health maintenance organizations (HMOs) in Israel have instituted a quality control mechanism to monitor health in its members and to promote prevention [19]. In Maccabi Healthcare Services (MHS) these are called health value added (HVA) indicators. For vascular diseases, a computerized registry contains updated real-time information on such clinical measures as low density lipoprotein (LDL)-cholesterol, blood pressure measurements, body mass index (BMI), AF, and other data related to the treatment of these diseases and their complications. Still to be assessed are the long-term effects of this technology on the health of the population as trends in disease management change over time, and the overall health of the population. It is therefore a public health interest to determine, as a first step, whether this database provides a useful description of the epidemiology of stroke and AF in a subset of the Israeli population, and how this profile compares to those reported from other countries.

The overall objective of this study was to describe the association of AF with stroke in Israel, using the MHS cardiovascular disease registry, and compare it to the existing literature. Specifically, we aimed to (i) estimate the prevalence of stroke within a defined population in the community, consisting of Maccabi patients, with or without AF, in the year 2010; and (ii) estimate the strength of association for AF and first stroke, with adjustment for various known risk factors, including hypertension, coronary heart disease, congestive heart failure (CHF), diabetes, dyslipidemia and history of TIA.

PATIENTS AND METHODS

MHS is the second largest health maintenance organization in Israel, providing medical care to approximately 1.9 million members, which is about one-quarter of Israel's population. The MHS cardiovascular database contains information on 102,964 Maccabi members (as of the year 2010) who carry a confirmed diagnosis of vascular disease, whether cardiac, cerebral, aortic or peripheral. This includes, among others, all patients who have AF or have had a stroke. The nature of the database does not distinguish between chronic (persistent) or paroxysmal (intermittent) AF. Clinical information in this database is derived from two sources: (i) diagnoses, laboratories, and examinations entered into the medical records by the physician using Clicks® documentation software; and (ii) hospital discharge codes. In addition to the diagnosis that led to members' inclusion in this database, additional clinical information including demographic variables, presence of AF and stroke, dates of onset, and other risk factors are recorded. This study was restricted to members 45 years or older, constituting 84,417 patients from the database, out of a total of 545,151 MHS members in this age group.

The study consisted of two parts: (i) a cross-sectional (prevalence) design using data drawn from the vascular database and population data of MHS, and (ii) a case-control study using patients diagnosed with stroke (cases) in the MHS database and a randomized sample of non-stroke (controls) drawn from the whole Maccabi population aged 45 years and older.

For the stroke prevalence part of this study, registry patients, namely all reported cases of first (new) stroke, were counted. For prevalence estimates, age-stratified population data from Maccabi were used for the denominator and were calculated separately for AF and non-AF members. Inclusion criteria were presence in the vascular database as of 1 January 2011 and age 45 and over. Exclusion criteria were incomplete or no information as of 1 January 2011 due to death or transfer to another HMO.

For the case-control study, all stroke patients were drawn from the vascular database. Cases included all 1074 registry patients who suffered a first stroke in the year 2010, based on a registry-confirmed diagnosis. The controls were a random, unmatched same-size sample of patients who did not suffer a first stroke prior to 2010, drawn from the general population of Maccabi members which included non-stroke registry patients as well. The SPSS algorithm was used for random selection among all MHS patients who did not have a stroke in 2010. A database was compiled of 544,077 Maccabi members aged 45 and up who had no stroke as of 2010. The SPSS random sampling procedure yielded a control sample of 1036 patients. The exposure was defined as presence of AF within 1 year prior to the stroke in cases, and anytime during the calendar year 2010 for controls.

For the case-control stage, the case inclusion criteria were: (i) membership of MHS in the vascular registry as of 1 January 2011, (ii) age 45 and over, and (iii) entrance into the database because of stroke in the calendar year 2010. The exclusion criteria were: (i) registry patients for whom there were no data on stroke or AF for the calendar year 2010, and (ii) death in the year 2010. For controls, inclusion criteria were: (i) membership in Maccabi as of 1 January 2011, and (ii) age 45 years or older. Exclusion criteria were: (i) presence in vascular database because of stroke as of 2010, and (ii) death in 2010.

Data collection was performed with the assistance of the Maccabi Medical Informatics and Services Evaluation departments. Statistical analysis was performed using SPSS© 19 (IBM Inc.) and Epi Info 7 (US Centers for Disease Control) software. Graphical illustrations were prepared using Microsoft Excel©. Data were collected for all patients in the registry from 1 January 2010 to 1 January 2011 and included: demographic information (date of birth, gender, area of residence), presence of and onset date of stroke or TIA, presence of AF, date of AF diagnosis, new stroke during 2010 with date of onset, history of heart failure, diagnosis of diabetes and/or hypertension, dyslipidemia as documented by diagnostic codes in the chart, history of coronary artery disease, and previous myocardial infarction (MI). The criteria for these diagnostic entries are standardized in the Medical Informatics Department.

Sample size was predetermined as we used all 1074 stroke patients in 2010. Using Winpepi software, the calculated power of the study was 97% to detect an estimated odds ratio for AF among stroke patients of 2, which is a very conservative estimate based on the risk ratios in the studies noted in the introduction. Approval of this study was obtained from the MHS Institutional Review Board. Since there were no personally identifiable patient data and no patient contact or intervention, informed consent was not required.

The dependent dichotomous variable was occurrence of stroke. Risk factors and presence of AF were dichotomous independent variables. BMI was treated as a continuous independent variable. For univariate analysis, five age categories were employed: 45–54, 55–64, 65–74, 75–85, and 85+. For description of the database, continuous variables were checked for normality and comparisons between groups were checked with either the *t*-test or the Mann-Whitney test as appropriate. Categorical variables were checked by the chi-square test.

Next, for univariate cross-sectional analysis, stroke prevalence rates were calculated for the AF and non-AF group using Maccabi population data for the non-exposed, non-stroke denominator. For stroke prevalence, all old and new stroke cases as of 2010 were counted. Because AF is a fairly stable diagnosis, for AF exposure, all cases of AF (without reference to time) were included. Using age-stratified data, odds ratios and confidence intervals were calculated for each age bracket, separately for males and females.

For the case-control step, univariate analysis was performed, comparing the prevalence of risk factors in stroke and non-stroke groups. Continuous variables were checked for appropriate measures of central tendency and variation. Separate analyses were performed for men and women. Next, based on significant associations found in univariate analysis, multivariable analysis using binary logistic regression was performed. We built a model using AF and other risk factors to find associations for the occurrence of stroke, adjusting for age as a continuous variable. Separate models were constructed for males and females, while other risk factors were entered as dichotomous variables. Independent variables were checked for collinearity, confounding, and interactions. Odds ratios (OR) and 95% confidence intervals (CI) were determined to show strength of association. Goodness of fit was evaluated using classification tables, the likelihood ratio test, Hosmer-Lemeshow test, and the C-statistic for receiver operating characteristic (ROC) analysis.

RESULTS

PREVALENCE

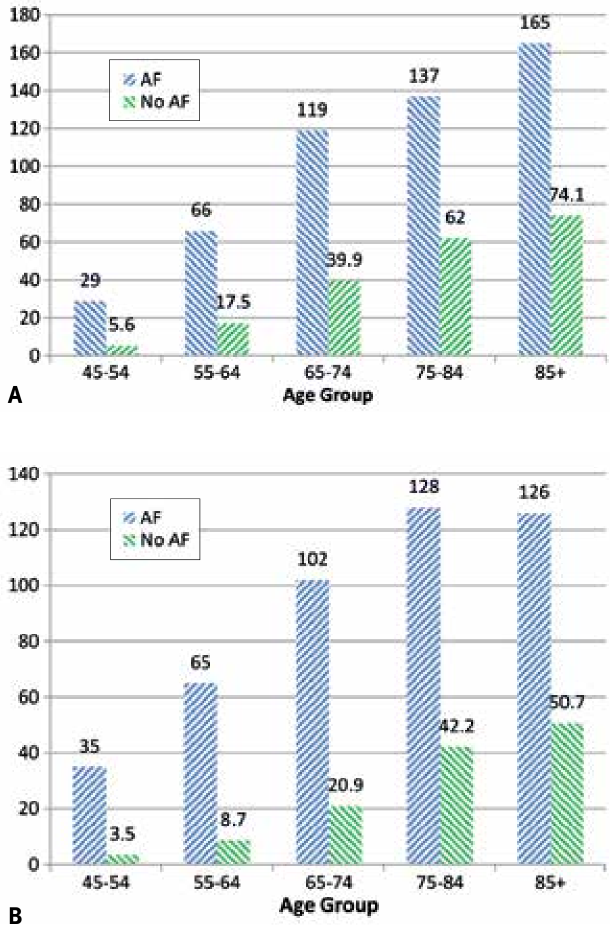
Overall descriptive statistics for the vascular database are shown in Table 1. For this purpose the database was divided into subjects with and without atrial fibrillation. The AF group was significantly older than the non-AF group (median 73 vs. 65, $P < 0.001$). This group had more women (46% vs. 35.4%, $P < 0.001$) and a higher mean BMI (29.6 vs 28.8, $P < 0.001$) than the non-AF group. As expected, significantly more AF patients were on anticoagulation (47.5% vs. 3.2%, $P < 0.001$). The proportion of each group with various risk factors and comorbidities is also shown. Paradoxically, several factors (dyslipidemia, stroke, diabetes) were present in higher frequencies in the non-AF group than in AF patients. This most likely reflects the criteria for patients' inclusion in the database, comprising the

Table 1. Descriptive data for the Maccabi Healthcare Services vascular database

Characteristic	AF (n=16,736)	Non-AF (n=67,681)	All (n=84,417)	*P* value*
Age, median (range)	73 (45–107)	65 (45–107)	67	‹ 0.001
CHF, % (n)	19.2 (3220)	7.4 (5016)	9.8 (8236)	‹ 0.001
Female, % (n)	46.3 (7745)	35.4 (23,955)	37.6 (31,700)	‹ 0.001
Diabetes, % (n)	30.5 (5110)	32.1 (21,741)	31.8 (26,851)	‹ 0.001
Takes anticoagulant, % (n)	47.5 (7946)	3.2 (2168)	12 (10,114)	‹ 0.001
Stroke, % (n)	10.6 (1775)	12.5 (8466)	12.1 (10,241)	‹ 0.001
Age				
45–54, % (n)	7.4 (1231)	17.1 (11,372)	15.2 (12,803)	‹ 0.001
55–64, % (n)	20.6 (3448)	30.9 (20,922)	28.9 (24,370)	
65–74, % (n)	29.3 (4898)	27.1 (20,922)	27.5 (23,223)	
75–84, % (n)	30.3 (5070)	18.9 (12,791)	21.2 (17,861)	
≥ 85, % (n)	12.5 (2089)	6.0 (4071)	7.3 (6160)	
BMI, kg/m², mean (SD)	29.6 (5.6)	28.8 (5)	28.9 (5.2)	‹ 0.001
Dyslipidemia, % (n)	38 (6315)	49.4 (33,412)	47.1 (39,777)	‹ 0.001
Hypertension, % (n)	78.2 (13,083)	67.8 (45,894)	69.9 (58,977)	‹ 0.001

*BMI, using unpaired *t*-test, age, Mann-Whitney test, all others were Pearson chi-square
% are columnar, i.e., proportion of AF with characteristic

Figure 1. Stroke prevalence by age in **[A]** men and **[B]** women



risk factors and comorbidities themselves (i.e., the occurrence of stroke results in inclusion in the database). Thus the non-AF group represents patients included in the database for reasons other than AF, and thus the proportions are not representative of the total HMO population of non-AF patients.

Stroke prevalence was calculated by counting the stroke events in the database (which contains all stroke patients) and using this sum as the numerator, while the relevant Maccabi population was used as the denominator (not shown). For the non-AF group, age-stratified Maccabi population data were obtained. The denominator for each stratum was determined by subtracting the number of AF patients for that age stratum (from the database) from the overall population size of the stratum. The result represents the overall non-AF population of Maccabi. The stroke prevalence rates for each gender, by presence of AF, are shown in Figures 1A and 1B. In both men and women the association with AF was strong and statistically significant, but decreased with older age. This trend can be seen clearly in the figures. The overall incidence of first stroke for the year 2010 in the studied age group was 19.75 cases/10,000.

Table 2. Prevalence of selected risk factors for stroke in Maccabi members aged 45 and older

Variable	Stroke (cases) N=1074	Non-stroke (controls) N=1036	*P* value*
Age, mean (SD), median, range	68.5 (11.7), 69, 45–99	58.7 (10.8), 56, 45–95	< 0.001
Female, % (n) (N=1042)	46.3 (497)	52.6 (545)	< 0.001
BMI, mean (SD)	28.6 (5.3)	28.4 (5.6)	0.25
Diabetes, % (n)(n=570)	36.2 (389)	17.5 (181)	< 0.001
Atrial Fibrillation, % (n) (n=233)	17.4 (187)	4.4 (46)	< 0.001
CHF, % (n)(n=109)	8 (86)	2.2 (23)	< 0.001
Prior MI, % (n) (n=185)	13.4 (144)	4 (41)	< 0.001
Hypertension, % (n) (n=1255)	75.6 (815)	42.5 (440)	< 0.001
Dyslipidemia, % (n) (n=868)	46.3 (497)	35.8 (371)	< 0.001
Anticoagulation (n=188)	14.8 (159)	2.8 (29)	< 0.001
Prior TIA, % (n) (n=143)	12.6 (135)	0.8 (8)	< 0.001

*Chi-square test for difference in proportions between groups for risk factors, unpaired t-test for BMI, Mann-Whitney test for age

For males, the age-specific prevalence ranges from 5.6 to 74.1 per thousand in non-AF patients, and 29–165 per thousand for AF patients. The association between AF and stroke prevalence was highest in the youngest group (OR 5.26, 95%CI 3.5–7.9, not shown). In women, the prevalence rates for the different age groups was lower than for men (range 3.5–50.7 per thousand), but the associated risk with AF was stronger than for men, especially in the youngest age group (OR 10.6, 95%CI 6–18.4).

STROKE RISK FACTORS

For the case-control study there were 1074 stroke cases and 1036 random unmatched controls. Univariate analysis of the frequency of risk factors is presented in Table 2. As can be seen, the stroke group was significantly older (median 69 vs. 56, $P < 0.001$) and had more males (53.7% vs 47.3%, $P < 0.001$) than the control group. All of the risk factors listed occurred in much higher frequencies in the stroke group, at the 0.001 significance level. In addition, the stroke group, as would be expected, had higher rates of anticoagulation treatment (14.8% vs. 2.8%, $P < 0.001$). There was no difference in the BMI levels between the two groups. Of note was the rate of missing values for the BMI variable (20%) with significantly more missing in the control group than the stroke group. We suspected that BMI data were Missing Not at Random (MNAR); therefore, this variable was not included in the subsequent analysis.

Multivariable analysis using binary logistic regression was performed using the variables found to be significant in the univariate analysis. For this purpose age was used as a continu-

Table 3. Association of various risk factors (OR, 95%CI) with stroke, both genders

Factor	OR	CI lower	CI upper	*P* value
Age (continuous)	1.05	1.04	1.06	‹ 0.001
Gender (female/male)	0.69	0.55	0.87	.001
Diabetes (yes/no)	1.54	1.20	1.97	.001
Hypertension (yes/no)	2.17	1.75	2.69	‹ 0.001
Dyslipidemia (yes/no)	1.29	1.03	1.61	0.027
Myocardial infarction (yes/no)	2.08	1.33	3.26	‹ 0.001
Atrial fibrillation (yes/no)	2.12	1.40	3.22	‹ 0.001
TIA (yes/no)	18.07	7.18	45.46	‹ 0.001

ROC area under the curve = 0.795
CHF not in model

ous variable in order to show a more refined effect for age and provide the best adjustment for other risk factors. The results are presented in Table 3. In the multivariate model, male gender and age remained significantly associated with stroke, even after adjustment for other risk factors. Each year of age added about 5–6% to risk of stroke. Similarly, in all models, AF, hypertension, diabetes, and history of TIA remained highly significant risk factors after adjustment for age and gender. Of note was the very strong association between prior TIA and new stroke (OR 9.92 for males, 21.03 for females, not shown). Unexpectedly, we found that history of congestive heart failure did not remain an independent risk factor after adjusting for other variables, despite a very large univariate effect. We also noted that among females, dyslipidemia and history of MI became non-significant after age adjustment, in contrast to the strong association in males.

DISCUSSION

To our knowledge this study is the first population-based analysis of prevalence of stroke in Israel, based on a large health HMO database. The World Health Organization (WHO) has placed priority on assessing the global burden of disease (GBD) for stroke [8]. GBD includes components not only of incidence, but also mortality, severity and duration, which allows a calculation of disability-adjusted life years. Therefore, the information represented in prevalence data is highly significant for stroke. The worldwide prevalence of stroke survivors, whether or not disabled as a result of the stroke, was estimated to be 62 million in 2005 and projected to rise to 67 million in 2015 and 77 million in 2030 [20].

In our study, approximately 5.3% of women and 7.5% of men over 75 are survivors of stroke. Among people with atrial fibrillation, this prevalence is approximately doubled. Although the association of AF and the incidence of stroke is well known, the association with prevalence is less obvious, because survival may be influenced by both the stroke and AF. Elsewhere in the world, prevalence studies have been published, but none of them classify by AF status. Review of these studies shows that Israel has a burden similar to that of many European countries. Truelsen at al. [21] published a review for the WHO in 2006 of stroke incidence and prevalence in European countries. In that study most countries showed a higher prevalence in men than in women, and a sharp increase with age similar to ours. Israel's relatively low prevalence rates are similar to those in Belgium, Cyprus and Germany, in contrast to the much higher rates in Finland, Greece, Portugal and the Czech Republic. Another review, by Zhang [22], of data from some European countries and the United States found that while stroke incidence (of all types) was higher in men, prevalence was similar between genders. His review also showed that stroke mortality rates were higher in men, possibly explaining the gender discrepancy in incidence but not prevalence.

Our case-control study is, to the best of our knowledge, the first of its type in Israel to examine the association of various risk factors with first stroke. O'Donnell et al. [12], in the large INTERSTROKE international case-control study, found risk factors for first stroke similar to our findings, in addition to smoking, physical activity, psychosocial stress and depression. Our study is consistent, in most respects, with the literature regarding known risk factors with one exception: gender. Although, as noted, stroke incidence in general is indeed higher in men than in women, this association did not reverse after adjustment for atrial fibrillation. In the newer CHADS2-VASc algorithm, female gender is a risk factor. Prior literature has been somewhat inconsistent on this point [23]. Nonetheless, the consensus in more recent studies and reviews is that female gender is indeed a risk factor in AF patients [24].

Our study has several strengths. Although the study population was not a random sample of the Israeli population as a whole, Maccabi members comprise approximately 25% of the country's population covering all geographic and demographic sectors. The large sample permitted good multivariable analysis given the large number of cases. The database uses uniform criteria for the outcomes and risk factors, minimizing a potential source of information bias.

We acknowledge that our study had some limitations. Prevalence was examined for one year only and thus cannot show trends. Additionally, given that AF and other risk factors influence stroke risk over a prolonged period, it is possible that our one-year time window did not accurately assess risk that would be evident over a longer period. The diagnoses of AF, stroke and the various covariates are drawn from physician- and hospital-determined codes in the medical records. This allows for the possibility of misclassification. Significantly, because of the nature of the registry we were unable to distinguish between hemorrhagic stroke and ischemic stroke, or to identify recurrent strokes and, therefore, could not estimate incidence for all strokes. In our study we were not able to distinguish between persistent and intermittent atrial fibrillation. Although some older studies have distinguished between them regarding risk of stroke, in the modern clinical rule schemes, such as CHADS2-VASc, this is not considered. Finally, not addressed by our study is the presence of other factors that could reduce the risk of stroke, such as the use of antihypertensive medication, statins and aspirin, as well as physical activity, all of which can partially mitigate the effects of the risk factors that were included.

CONCLUSIONS

Our analysis of the Maccabi Healthcare Services vascular database yielded prevalence information and association estimates of known risk factors with stroke, which are consistent with the epidemiological literature from Europe and the U.S. Analysis of HMO database information, such as that collected by Maccabi, is a useful method for studying the epidemiology of stroke and its association with various risk factors. Improvements in the database over time, including the ability to track secondary strokes, would allow a cohort (survival) study to be conducted, which would better characterize the risk factors and their association with stroke, and allow proper estimation of incidence and tracking its change over time.

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References

1. Treger I, Shames J, Giaquinto S, Ring H. Return to work in stroke patients. *Disabil Rehabil* 2007; 29 (17): 1397-403.
2. O'Donnell M, Xavier D, Diener C, et al. Rationale and design of INTERSTROKE: a global case-control study of risk factors for stroke. *Neuroepidemiology* 2010; 35 (1): 36-44.
3. Israel Central Bureau of Statistics. Health Survey 2009. 2009; Available at: http://www.cbs.gov.il/www/briut/briut09/t19.xls. Accessed Dec 2011.
4. Tanne D, Bornstein NM. National Acute Stroke Israel Survey (NASIS) 2010. December 2010.
5. Carandang R, Seshadri S, Beiser A, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA* 2006; 296 (24): 2939-46.
6. Ingall T. Stroke – incidence, mortality, morbidity and risk. *J Insur Med* 2004; 36 (2): 143-52.
7. Hong KS, Yegiaian S, Lee M, Lee J, Saver JL. Declining stroke and vascular event recurrence rates in secondary prevention trials over the past 50 years and consequences for current trial design. *Circulation* 2011; 123 (19): 2111-19.
8. World Health Organization. Global Burden of Disease. Available at: http://www.who.int/topics/global_burden_of_disease/en/. Accessed 5.8.2014.
9. Haratz S, Tanne D. Diabetes, hyperglycemia and the management of cerebrovascular disease. *Curr Opin Neurol* 2011; 24 (1): 81-8.
10. Sharma M, Hakim AM. The management of hypertension for primary stroke prevention: a proposed approach. *Int J Stroke* 2011; 6 (2): 144-9.
11. Prinz V, Endres M. Statins and stroke: prevention and beyond. *Curr Opin Neurol* 2011; 24 (1): 75-80.
12. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; 376 (9735): 112-23.
13. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European Perspective. *Clin Epideimiol* 2014; 6: 213-20.
14. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; 285 (22): 2864-70.
15. Stroke Risk in Atrial Fibrillation Working Group. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. *Stroke* 2008; 39 (6): 1901-10.
16. Gage B, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation* 2004; 110 (16): 2287-92.
17. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012; 33 (12): 1500-10.
18. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. *J Am Coll Cardiol* (2014); 64 (21): e1-76.
19. Israel Ministry of Health. The National Program for Health Outcome Measures: Report for 2007-2009. April 2011.
20. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol* 2007; 6 (2): 182-7.
21. Truelsen T, Piechowski-Jozwiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. *Eur J Neurol* 2006; 13 (6): 581-98.
22. Zhang Y, Chapman AM, Plested M, Jackson D, Purroy F. The incidence, prevalence, and mortality of stroke in France, Germany, Italy, Spain, the UK, and the US: a literature review. *Stroke Res Treat* 2012; 2012: 436125.
23. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007; 69 (6): 546-54.
24. Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ* 2012; 344: e3522.

"I believe the greatest gift I can conceive of having from anyone is to be seen, heard, understood, and touched by them. The greatest gift I can give is to see, hear, understand, and touch another person"

Virginia Satir (1916-1988), American social worker and author, known especially for her approach to family therapy and her work with family reconstruction. She is also known for creating the Virginia Satir Change Process Model, a psychological model developed through clinical studies. Change management and organizational gurus of the 1990s and 2000s embrace this model to define how change impacts organizations