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Systematic Review

A Comprehensive Systematic Review and Meta-analysis on the Risk Factors of Stroke in Iranian Population

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Abstract

Background: There are limited data on vascular risk factors (VRFs) in low- and middle-income countries (LMICs). This meta-analysis was completed to summarize the existing evidence on stroke risk factors (SRFs) in the Iranian population.

Methods: An electronic literature search of the databases including PubMed, Embase, Web of Science, Scopus, Scientific Information Database (SID), Magiran, and IranMedex was performed to identify the related articles published up to March 2018. For categorical or continuous variables, the data were also pooled using the fixed- or the random-effect models, respectively, expressed as odds ratio (OR) or weighted mean difference (WMD).

Results: A total of 15 articles were recruited. The risk of stroke was associated with mean age, but not gender. Among traditional VRFs, hypertension (HTN), systolic and diastolic blood pressure (DBP), diabetes mellitus (DM), and fasting blood glucose (FBG) were associated with increased risk of stroke. Apart from the high circulating levels of triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), and low high-density lipoprotein-cholesterol (HDL-C), other potential risk factors namely cigarette smoking (CS), opioid addiction (OD), and waist circumference (WC) were identified to be independent stroke determinants.

Conclusion: The present systematic review and meta-analysis provided a summary of the most important SRFs, which are potentially modifiable and preventable. Overall, Iran, similar to many other LMICs, is experiencing an ever-increasing rate of stroke-prone elderly people. The LMICs are thus suggested to develop national approaches to recognize and address VRFs, to monitor and control CS and OD rates, and to encourage a healthy lifestyle.

Keywords: Iran, Low- and middle-income countries, Meta-analysis, Risk factor, Stroke

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Introduction

Stroke, with its main types including ischemic and hemorrhagic, is known as the second leading cause of death and the fourth leading cause of mortality worldwide; thus, approximately 5.7 million deaths are recorded annually due to this medical condition, accounting for 9.7% of all-cause mortality across the world.[1,2] It also occurs in 1–3 cases per thousand people each year in developed countries,[3] and it is growing in Iran, affecting 372 people per 100 000 population.[4] The reports in this respect have also demonstrated that age-standardized stroke mortality have totally decreased in the past two decades. However, the absolute number of individuals experiencing a stroke every year, as well as stroke survivors, related deaths, and the overall global burden of this condition (i.e., the disability-adjusted life years: DALYs lost) have been great and increasing, especially in low- and middle-income countries (LMICs) over the past decades.[5] The LMICs also account for more than 85% of strokes correlated with mortality and morbidity, leading to the highest disease burden in these countries. In addition, geographic variations can add to the epidemiology of the stroke, as the highest incidence and prevalence rates are being reported in the same nations.[6]

Determining potential stroke risk factors (SRFs) within each geographical and ethnic region is accordingly of

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utmost importance to adjust stroke prevention programs based on existing needs and facilities.[7,8] Previously, it had been reported that there could be regional variations in the significance of risk factors, which had in turn resulted in worldwide discrepancies observed in incidence rate and subtypes of stroke.[9] Recently, the INTERSTROKE, a large-scale case-control study of SRFs in 32 countries, has reported 10 potentially modifiable risk factors for either ischemic or hemorrhagic stroke, associated with 90% population attributable risks of stroke in each major geographical region of the world as well as in specific age and gender groups.[10,11] The regional variations of SRFs are thus of great importance for risk stratification and lifestyle modification programs in each region. In this way, analysis of SRFs should be conducted in different regional and ethnic groups in order to specify stroke prevention programs and increase their success rates.[2]

Iran, as a populous LMIC located in the Middle East with considerably diverse ethnic groups and social classes, largely reflects the core of such countries. In addition, the relatively younger age of stroke in Iran (approximately one decade earlier in Iran than that in Western countries) can significantly increase stroke DALYs.[12] Thus, providing better evidence on SRFs in the Iranian population as an LMIC is particularly relevant. Although several studies have previously addressed the analysis of SRFs in the Iranian population, there are variations in methodologies and sample sizes, restricting their implications to develop a nationwide stroke prevention program based on a risk stratification model.[13-19] With this purpose in mind and given the unavailability of structured studies, pooling literature data, the present systematic review and meta-analysis was undertaken to determine SRFs in the Iranian population.

Materials and Methods

This meta-analysis was designed and performed according to the guidelines in the preferred reporting items for systematic reviews and meta-analyses (PRISMA).

Search Strategy

As the main strategy, two authors independently searched international and national databases including PubMed, Embase, Web of Science, Scopus, Scientific Information Database (SID), Magiran, and IranMedex for relevant articles published until March 2018. The searches were also conducted using the following MeSH terms and text words as well as their Persian equivalents: ["stroke" OR "brain infarction" OR "ischemic stroke" OR "intracerebral hemorrhagic' OR "intracranial bleed" OR "hemorrhagic stroke" OR "subarachnoid hemorrhage" OR "cerebrovascular disorders" OR "cerebrovascular disease"] AND ["all related risk factors" (such as demographic, anthropometric, vascular, diabetes mellitus, hypertension, cigarette smoking, opioid dependence, and hyperlipidemia

factors)] AND ["Iran" OR "Iranian"].

In order to augment the sensitivity of the search strategy, the reference lists of the included articles were manually screened out to detect any additional relevant studies and even Google Scholar as a gray literature was hand-scanned. The searches were restricted to observational studies published in the English or Persian literature without any limitations in their publication date.

Definitions

Most of the investigated SRFs had similar definitions in national and international publications. However, the authors used the definitions of SRFs across selected articles as included here: hypertension (HTN) HTN represented systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg or taking anti-hypertensive medications.[20] Diabetes mellitus (DM) was defined as fasting blood glucose (FBG) ≥ 7 mmol/L, 2 h-PG ≥ 11.1 mmol/L or current intake of anti-diabetic medicines.[20] Cigarette smoking (CS) represented current or past use of cigarettes or any other type of pipes or smoking instruments,[20] and family history of cardiovascular diseases (CVDs) was described as any prior diagnosis of CVDs in first-degree relatives.[20] Also, body mass index (BMI) was weight divided by height squared (kg/m^2) and waist circumference (WC) was measured in a standing position at the point midway between the lowest rib and the iliac crest in both genders[21]. Opioid dependence (OD) was defined according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) (304.00, opium dependence): continued for at least one year (via inhalation or oral ingestion).[22] Furthermore, total-cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), and FBG levels in serum were further considered.

Inclusion and Exclusion Criteria

Studies meeting the eligibility criteria including observational human studies with cross-sectional, case-control, or cohort designs as well as articles investigating associations between related risk factors and stroke were selected for this study. Moreover, studies published until March 2018, without any limitations on their sample size, were found eligible. We used articles reporting sufficient data to extract the number of events for calculating odds ratios (ORs) or weighted mean differences (WMDs) with 95% confidence intervals (CIs) for the related risk factors in patients with first-ever stroke, compared with control groups without any strokes or related CVDs. However, in-vitro studies, animal experiments, case reports, review articles, and seminar abstracts with no full-texts, together with studies that had not obtained the least required scores of the quality assessment process were excluded.

Data Extraction and Quality Assessment

Two independent authors (RT and BK) extracted the data from the retrieved articles and imported them into standard forms in the Microsoft Excel spreadsheets. Accordingly, the extracted information included first author's name, date published, study setting, participants' demographic characteristics, sample size (either in stroke patients or control group), study design, stroke type, risk factors, and required data to estimate ORs or WMDs and 95% CIs for risk factors if they were categorical or continuous variables, respectively, in stroke patients and control groups. The quality of the given studies was also assessed by two independent authors (RT and BK) according to a comprehensive quality assessment using the Newcastle-Ottawa Scale, comprised of eight and six items for cohort/case-control and cross-sectional studies, respectively. These items had covered three aspects including selection, comparability, and exposure. The selected study obtaining 4-6 points could be considered as an article of moderate quality and the one with more than 6 points could be assigned as high quality.

In case of disagreements in the domains of data extraction and quality assessment, RT and BK discussed to reach consensus or resolved the disagreement through talks with a third author (A-BH).

Data Synthesis and Statistical Analysis

All the statistical analyses were performed using the Stata (version 12.0) (Stata Corp., College Station, TX) software package. The association between the related risk factors and the risk of stroke was also estimated. To assess the overall pooled effect sizes (ESs), unadjusted ORs or WMDs were respectively employed with 95% CIs for continuous or categorical factors. The Cochran Q test and the I-squared (I^2) test were further utilized to measure heterogeneity across the included studies. According to the heterogeneity findings, whenever $I^2 \geq 50\%$ and $P < 0.05$, a random-effect model using the DerSimonian and Laird method could be applied to combine the studies, a fixed-effect model could be also implemented using the Mantel and Haenszel method provided that $I^2 < 50\%$ and $P > 0.05$. The sensitivity analysis was additionally conducted to examine the impact of each study on the overall pooled ESs after excluding each one using the leave-one-out method. Subgroup analyses were also completed to identify the possible sources of heterogeneity regarding the following moderator variables: type of controls (healthy vs. hospital-based control), type of stroke (all vs. ischemic vs. hemorrhagic stroke), study design (cross-sectional vs. cohort vs. case-control study), and matching status (non-matching vs. gender or age matching). The Begg's and the Egger's tests were consequently utilized to evaluate the possibility of publication bias. The two-tailed P 0.05 was also considered as statistically significant.

Results

Characteristics of Selected Studies

In the first step searching the online databases, 573 articles related to SRFs were identified. After removing the duplicates and the irrelevant ones, 15 studies (namely, 10 case-control, three cohort, and two cross-sectional studies) were selected for the current meta-analysis. The flowchart details of the systematic process of study identification and selection are summarized in Figure 1. The sample size in the selected studies included 13 342 participants (10 009 ischemic, 255 hemorrhagic, and 3078 all stroke) ranging from 72 to 5398 cases. The selected articles had been published from 2003 up to March 2018. The characteristics of the observational studies included are presented in Table 1.

Main Outcomes

Forest plots reporting the meta-analysis of the included studies on SRFs consisting of demographic, traditional vascular, and life-style factors are illustrated in Figures 2 and 3.

The pooled findings showed that 13 factors influenced the risk of stroke in the Iranian population. As compared with the control group, the risk of stroke was correlated with the mean age (WMD = 5.49 years; 95% CI, 4.45, 6.56; $P < 0.001$; I^2: 45.4%) of the patients. Nevertheless, there was no significant relationship between gender (OR = 1.23; 95% CI, 0.85, 1.79; $P = 0.272$; I^2: 65.8%) and risk of stroke.

Among the traditional vascular risk factors (VRFs), HTN (OR = 3.56; 95% CI, 3.00, 4.23; $P < 0.001$; I^2: 37.7%), SBP (WMD = 13.42 mmHg; 95% CI, 10.19, 16.64; $P < 0.001$; I^2:0.0%), DBP (WMD = 6.66 mm Hg; 95% CI, 4.61, 8.70; $P < 0.001$; I^2:0.0%), and DM (OR = 2.15; 95% CI, 1.41, 3.29; $P < 0.001$; I^2: 74.4%) were the ones increasing the risk of stroke. Also, high levels of FBG (WMD = 36.86 mg/dL; 95% CI, 7.66, 66.07; $P = 0.013$; I^2: 89.5%), TG (WMD = 21.48 mg/dL; 95% CI, 10.03, 32.94; $P < 0.001$; I^2: 60.9%), TC (WMD = 15.08 mg/dL; 95% CI, 0.48, 29.68; $P = 0.043$; I^2: 86.9%), LDL-C levels (WMD = 23.89 mg/dL; 95% CI, 0.93, 46.84; $P = 0.041$; I^2: 94.9%), and low levels of HDL-C (WMD = -2.31 mg/dL; 95% CI, -4.30, -0.33; $P = 0.023$; I^2: 14.24%) were other factors affecting the risk of stroke. Based on two included articles, no significant association was found between family history of CVDs (OR = 1.94; 95% CI, 0.94, 4.06; $P = 0.077$; I^2: 51.1%) and risk of stroke. Life-style factors including OD (OR = 3.00; 95% CI, 1.81, 4.98; $P < 0.001$; I^2: 0.0%) and CS (OR = 1.44; 95% CI, 1.02, 2.03; $P = 0.038$; I^2: 64.0%) had further augmented the risk of stroke. However, WC (WMD = 3.25 CM; 95% CI, 1.44, 5.06; $P < 0.001$; I^2: 27.7%) was associated with stroke. There was also no significant relationship between BMI (WMD = 0.05 kg/m²; 95% CI, -1.41, 1.50; $P = 0.949$; I^2: 79.9%) and risk of stroke (Table 2).
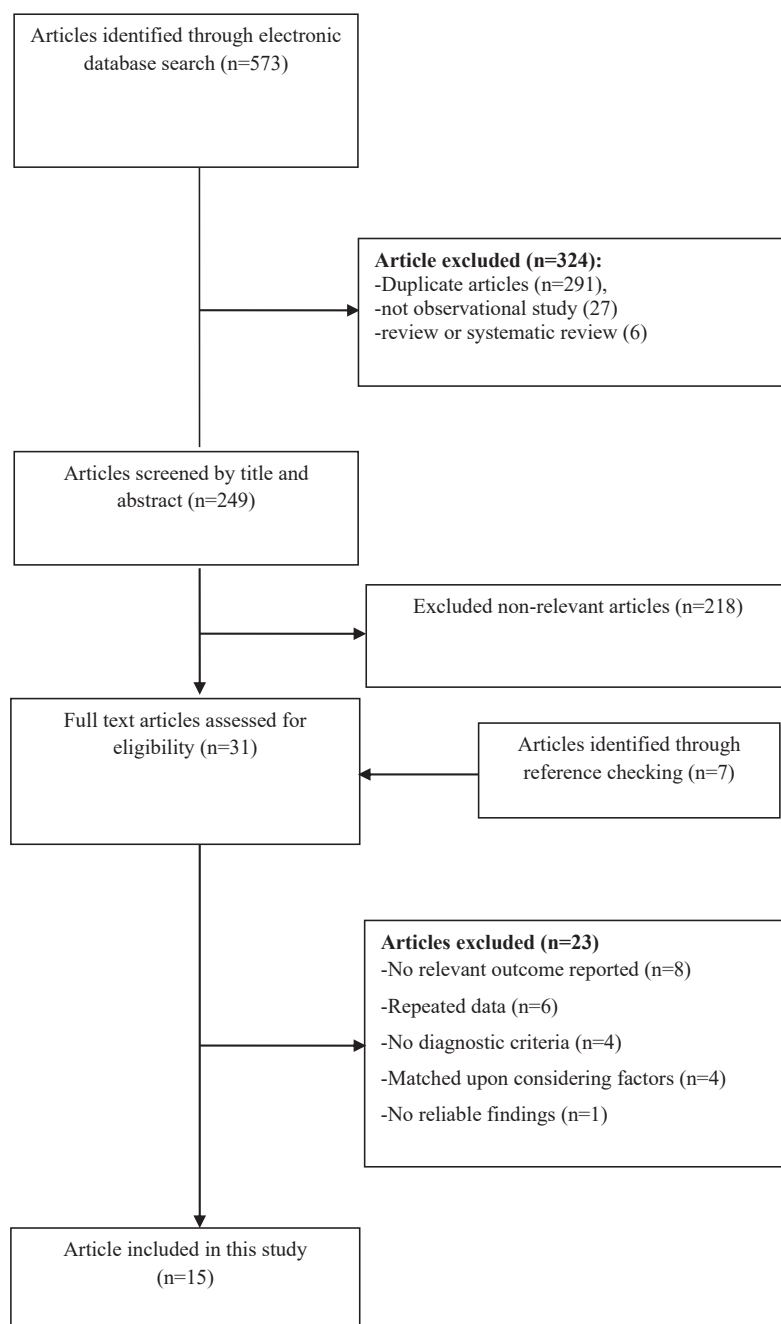
Figure 1. Literature Search and Review Flowchart for Selection of Studies.

Subgroup and Sensitivity Analyses

Subgroup analyses were conducted to identify the effects of moderator variables, i.e. type of control, stroke, study design, and matching status on heterogeneity statistics. The reduction of heterogeneity was demonstrated in some strata of the subgroups as shown in Table 2.

In subgroup analyses for gender, a significant association was observed between male gender and increased risk of stroke in studies with all types of stroke (OR = 1.71, 95% CI: 1.26, 2.33) and the ones with non-matching participants (OR = 1.39, 95% CI: 1.09, 1.77), compared with other groups. With regard to CS and risk of stroke, there was also a significant relationship in studies with all types of stroke (OR = 2.72, 95% CI: 1.75, 4.24) and cross-sectional ones (OR = 2.25, 95% CI: 1.19, 4.23) vs. studies with other strata. The findings correspondingly indicated a significant rising trend in TG levels in patients with stroke in studies with healthy control (WMD = 24.48 mg/dL; 95% CI 10.15, 38.81) and case-control ones (WMD = 23.99 mg/dL; 95% CI 7.46, 40.51), in comparison with other strata. Considering TC levels, there was a significant growth in patients with stroke in case-control studies with gender or age matching (WMD = 21.23 mg/dL; 95% CI 2.16, 40.30), compared with other strata. There was also a significant association in terms of the increased risk of stroke and LDL-C levels (WMD = 41.63 mg/dL; 95%

Table 1. Characteristics of Included Studies

Authors (Ref)	Publication Year	Sample size (case/control)	City	None of Female/Male	Type of Stroke Group/Control Groups	Age (Control, Case)	Study Design	Type of Analysis	Matching Factors	Factors included in Meta-analysis (based on reported primary data on article)
Fahimfar et al[14]	2012	69/2309	Tehran	1089/1289	All/ Healthy controls	60.19±7.11 Overall	CS	Adjusted with Cox proportional hazards regression (age, sex, smoking, HTN, DM)	Non-matching	Sex
Saneei et al[23]	2014	195/195	Isfahan	283/107	All/ Hospital based controls	61.5±11.17, 67.9±13.96	CCS	Unadjusted	Non-matching	Mean age, BMI, sex, HTN, smoking
Moshayedi et al[21]	2014	110/110	Tabriz	82/138	IS/ Hospital based controls	66.51±11.27, 66.42±11.31	CCS	Unadjusted	Mean age and sex	WC, HDL-c, LDL-c, TG, BMI, HTN, DM, and smoking,
Maghbooli et al[24]	2012	50/50	Zanjan	46/54	IS/ Hospital based controls	(60.42±10.35, 68.24±6.22)	CSS	Adjusted with logistic Regression (age, HTN, Smoking, TG,HDL)	Non-matching	Mean age, HDL-c, LDL-c, TC, and sex
Sadreddini et al[25]	2007	100/100	Tabriz	108/92	IS/ Healthy controls	67 ± 15 Overall	CCS	Unadjusted	Mean age and sex	HDL-c, LDL-c, TG, and TC
Parizadeh et al[20]	2017	106/2982	Tehran	1626/1462	IS/ Healthy controls	(64.4±7.3, 60.0±7.5)	CS	Adjusted with Cox hazards regression (Age, WC, DBP, SBP, FBS, Gender, smoking, FH CVD)	Non-matching	Mean age, SBP, DBP, FBG, WC, HDL-c, TC, BMI, sex, HTN, DM, smoking, and family history of CVD
Hosinian et al[16]	2016	60/60	Babol	48/72	IS/ Healthy controls	(62.0±6.7, 64.0±7.20)	CCS	Unadjusted	Mean age and sex	SBG, DBP, HDL-c, TG, TC, HTN, DM, and smoking
Ashjazadeh et al[26]	2013	171/86	Shiraz	109/148	IS/ Hospital based controls	(68.7±8.4, 67.9±13.3)	CCS	Unadjusted	Mean age and sex	HTN, DM, and smoking
Hesami et al[15]	2015	120/135	Tehran	116/139	HS/ Hospital based controls	(70.5±12.6, 67.5±12.7)	CCS	Unadjusted	Mean age and sex	HTN, DM, smoking
Sarrafzadegan et al[27]	2017	91/5307	Multicenter	2769/2629	IS/ Healthy controls	(50.57±11.6, 57.19±11.61)	CS	Adjusted with Cox proportional hazards regression (Current smoking, advanced age)	Non-matching	Mean age, SBP, DBP, FBG, WC, HDL-c, LDL-c, TG, BMI, sex, HTN, DM, and smoking
Saberi et al[22]	2016	83/83	Guilan	70/96	IS/ Healthy controls	(67.94±13.55, 68.55±15.01)	CSS	Adjusted with logistic regression (opium addiction, smoking, HTN, HX of stoke, Gender (male))	Mean age and sex	HTN, DM, smoking, and total addiction
Afshari et al[28]	2015	36/36	Ahvaz	14/58	IS/ Hospital based controls	(63.38±6.14, 65.1±14.37)	CCS	Adjusted with conditional logistic regression (HTN,CVD, LDL)	Mean age, BMI, smoking, and DM	FBG, HDL-c, LDL-c, TG, TC, sex, and HTN
Hamzehee-Moghadam et al[29]	2006	105/105	Kerman	110/100	All/ Hospital based controls	(66.6±11.4, 67.2±9.3)	CCS	Adjusted with logistic regression (smoking and opium)	Mean age and sex	Smoking and total addiction
Savadi-Oskouei et al[30]	2003	62/62	Ardabil	124/-	IS/ Hospital based controls	60.6 Overall	CCS	Unadjusted	Mean age and sex	HTN, DM, smoking, and family history of CVD
Savadi-Oskouei et al[31]	2004	132/132	Ardabil	124/140	IS/ Hospital based controls	64.6 Overall	CCS	Unadjusted	Mean age and sex	TG and TC

IS, Ischemic stroke; HS, Hemorrhage stroke; HC, Healthy controls; HBC, Hospital-based control; CS, Cohort Study; CCS, Case-control study; CSS, Cross-sectional study; BMI, Body mass index; WC, Waist circumference; FB, Fasting blood glucose; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TG, triglycerides; TC, Total-cholesterol; LDL-c, Low-density lipoprotein-cholesterol; HDL-c, High-density lipoprotein-cholesterol; DM, Diabetes mellitus; HTN, Hypertension.
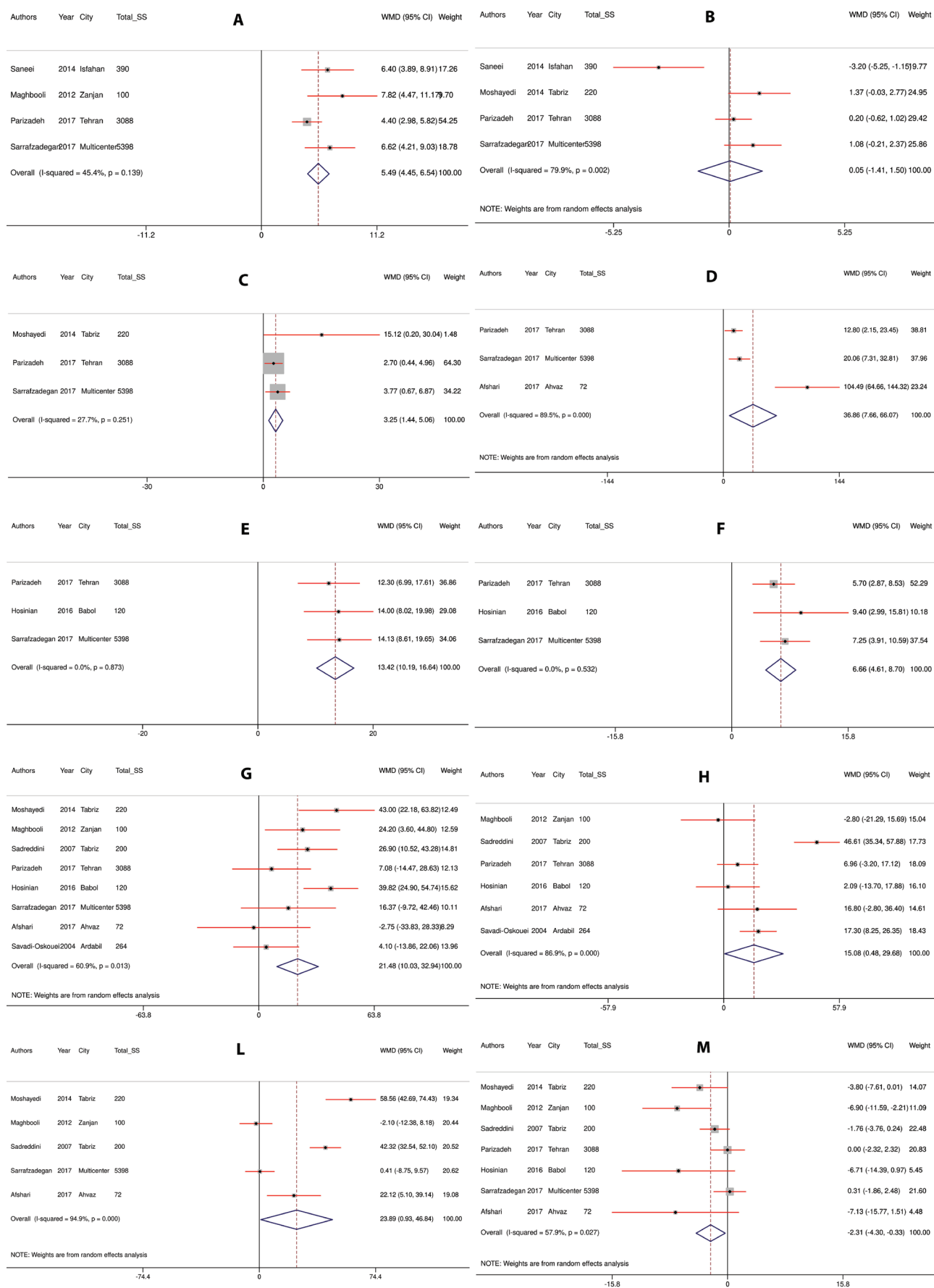
Figure 2. Meta-analysis of Stroke Factors Using Weighted Mean Differences Estimates for **A)** mean Age, **B)** BMI, **C)** WC, **D)** FBG, **E)** SBP, **F)** DBP, **G)** TG, **H)** TC, **L)** LDL-C, and **M)** HDL-C in the Stroke Patients and Control Groups (CI = 95%).
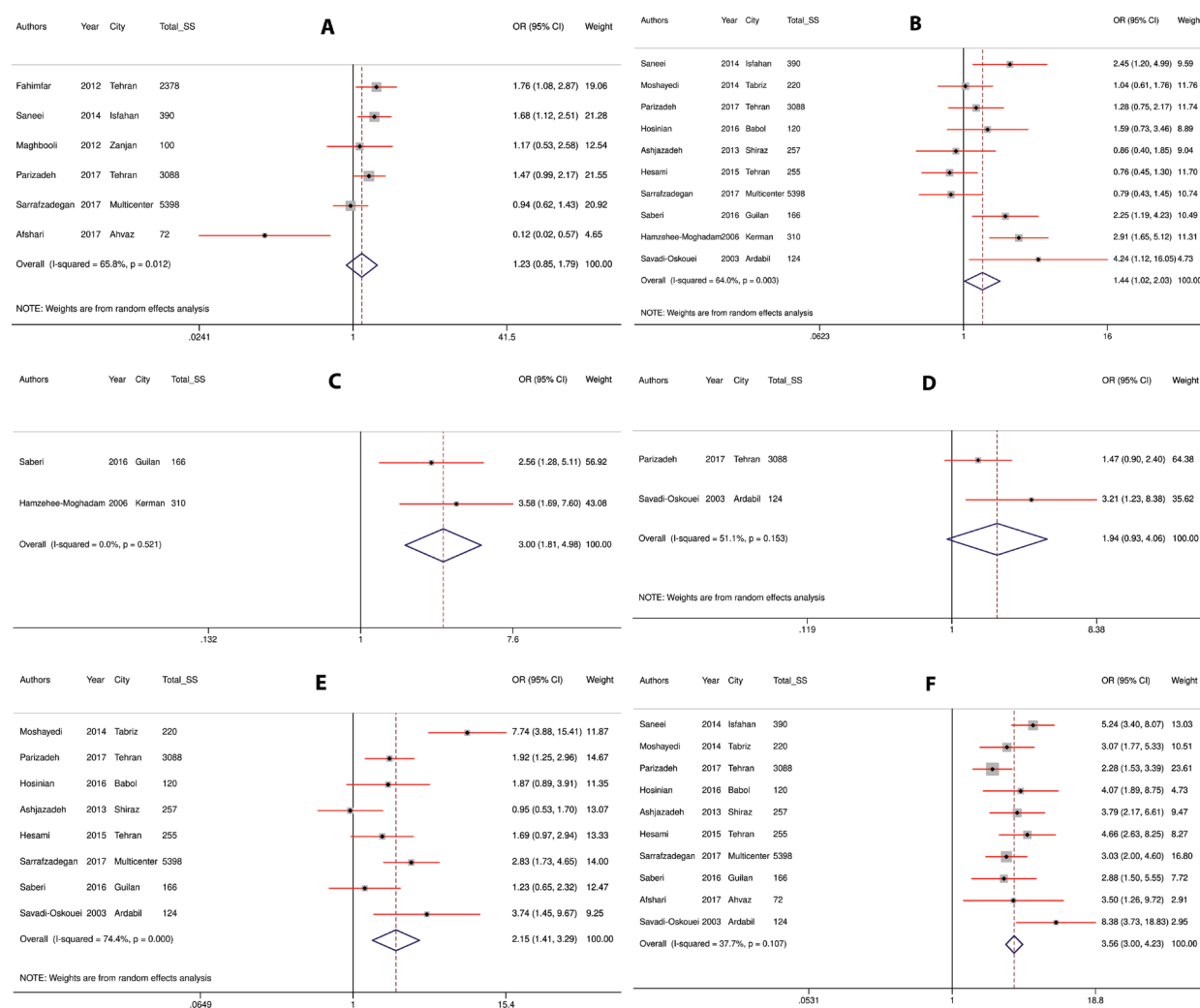
Figure 3. Meta-analysis of Stroke Factors Using Odds Ratios (ORs) Estimates for A) Sex, **B)** Smoking, **C)** Opioid Dependency, **D)** Family Hx of CVD, **E)** DM, and **F)** HTN in the Stroke Patients and Control Groups (CI=95%).

CI 23.63, 58.93). For low HDL-C levels, there was a significant decrease in patients with stroke in studies with hospital-based controls (WMD = -5.25 mg/dL; 95% CI -8.05, -2.45), the ones designed with case-control groups, and gender or age matching (WMD = -2.77 mg/dL; 95% CI -4.67, -0.87) in comparison with other strata.

After excluding several studies from the sensitivity analysis, the results revealed that the relationship between gender, CS, FBG, TC, LDL-C, and low levels of HDL-C and the risk of stroke had changed significantly upon respectively excluding the articles by Afshari et al,[28] Hamzehee-Moghadam et al,[29] Parizadeh et al,[20] Savadi-Oskouei et al,[31] Moshayedi et al,[21] and Maghbooli et al.[24] The association between CS, FBG, and HDL-C levels and the risk of stroke also changed significantly after removing more than one study.

For the remaining factors, there was no significant change between the pre- and post-sensitivity WMDs or ORs. The lower and the higher pooled WMDs or ORs in the sensitivity analyses are presented in Table 3.

Publication Bias and Quality Assessment

The Begg's and the Egger's tests showed that publication bias had affected only four factors in the studies on the Iranian population, which included mean age (P Begg's test = 0.17, P Egger's test < 0.01), FBG levels (P_{Bg} = 0.11, P_{Ee} = 0.01), WC (P_{Bg} = 0.11, P_{Ee} = 0.04), and low levels of HDL-C (P_{Bg} = 0.09, P_{Ee} = 0.02). Non-parametric methods (i.e., Duval and Tweedie' Trim and Fill method) were further utilized to compute the findings of the removed observational studies for two factors; however, the pooled ESs for the related factors did not change significantly after using the method.

Likewise, quality assessment using the Newcastle-Ottawa Scale established that 86.67% of the selected primary studies obtained at least two stars for selection, 100% of these articles were assigned with at least one star for comparability, and 93.34% of the primary studies included were given at least two stars for exposure category. The detailed quality assessment results are summarized in Table 4.

Table 2. Results of Overall and Subgroup Meta-analyses for Estimating the Association Between Risk Factors and Stroke

Variables			K*	I² (%)	Q test	Pooled ES (95% CI)	P Value
Mean age (year)	Total		4	45.4	5.49	5.49 (4.45, 6.56)^{WMD}	<0.001
Sex (male vs. female)	Total		6	65.8	14.60	1.23 (0.85, 1.79)^{OR}	0.272
	Type of control	Healthy controls	3	52.0	4.17	1.33 (0.93, 1.90)^{OR}	0.118
		Hospital-based controls	3	80.9	10.49	0.81 (0.27, 2.39)^{OR}	0.701
	Type of stroke	All	2	0.0	0.02	1.71 (1.26, 2.33)^{OR}	0.001
		IS	4	71.0	10.35	0.94 (0.53, 1.67)^{OR}	0.824
		HS	-	-	-	-	-
	Study design	Cohort	3	52.0	4.17	1.33 (0.93, 1.90)^{OR}	0.118
		Case-control	2	90.3	10.34	0.50 (0.40, 6.84)^{OR}	0.602
		Cross-sectional	1	-	0.00	1.17 (0.53, 2.58)^{OR}	0.688
	Matching	Non-matching	5	25.6	5.38	1.39 (1.09, 1.77)^{OR}	0.007
		Age matching	1	-	0.00	0.12 (0.02, 0.57)^{OR}	0.008
Smoking (Yes vs. No)	Total		10	64.0	24.97	1.44 (1.02, 2.03)^{OR}	0.038
	Type of control	Healthy controls	4	47.5	5.72	1.35 (0.88, 2.09)^{OR}	0.172
		Hospital-based controls	6	74.0	19.22	1.53 (0.89, 2.62)^{OR}	0.124
	Type of stroke	All	2	0.0	0.14	2.72 (1.75, 4.24)^{OR}	<0.001
		IS	7	42.9	10.52	1.29 (0.92, 1.82)^{OR}	0.136
		HS	1	-	0.00	0.76 (0.45, 1.30)^{OR}	0.325
	Study design	Cohort	2	28.0	1.39	1.03 (0.64, 1.65)^{OR}	0.915
		Case-control	7	68.9	19.31	1.53 (0.96, 2.43)^{OR}	0.075
		Cross-sectional	1	-	0.00	2.25 (1.19, 4.23)^{OR}	0.012
	Matching	Non-matching	3	64.6	5.65	1.32 (0.73, 2.39)^{OR}	0.365
		Sex or age matching	7	68.5	19.06	1.51 (0.96, 2.38)^{OR}	0.075
Opioid dependency (Yes vs. No)	Total		2	0.00	0.41	3.00 (1.81, 4.98)^{OR}	<0.001
Family Hx of CVD (Yes vs. No)	Total		2	51.1	2.04	1.94 (0.93, 4.06)^{OR}	0.077
BMI (kg/m²)	Total		4	79.9	14.96	0.05 (-1.41, 1.50)^{WMD}	0.949
	Type of control	Healthy controls	2	21.9	1.28	0.49 (-0.32, 1.31)^{WMD}	0.234
		Hospital-based controls	2	92.3	13.07	-0.83 (-5.33, 3.63)^{WMD}	0.709
	Type of stroke	All	1	-	0.00	-3.20 (-5.25, -1.15)^{WMD}	0.002
		IS	3	23.4	2.61	0.70 (-0.04, 1.44)^{WMD}	0.062
		HS	-	-	-	-	-
	Study design	Cohort	2	21.9	1.28	0.49 (-0.32, 1.31)^{WMD}	0.234
		Case-control	2	92.3	13.07	-0.85 (-5.33, 3.63)^{WMD}	0.709
		Cross-sectional	-	-	-	-	-
	Matching	Non-matching	3	83.7	12.28	-0.43 (-2.31, 1.44)^{WMD}	0.649
		Sex or age matching	1	-	0.00	1.37 (-0.03, 2.77)^{WMD}	0.055
WC (cm)	Total		3	27.7	2.77	3.25 (1.44, 5.06)^{WMD}	<0.001
FBG (mg/dL)	Total		3	89.5	19.02	36.86 (7.66, 66.07)^{WMD}	0.013
	Type of control	Healthy controls	2	0.0	0.73	15.78 (7.61, 23.96)^{WMD}	<0.001
		Hospital-based controls	1	-	0.00	104.49 (64.66, 144.32)^{WMD}	<0.001
	Type of stroke	All	-	-	-	-	-
		IS	3	89.5	19.02	36.86 (7.66, 66.07)^{WMD}	0.013
		HS	-	-	-	-	-
	Study design	Cohort	2	0.0	0.73	15.78 (7.61, 23.96)^{WMD}	<0.001
		Case-control	1	-	0.00	104.49 (64.66, 144.32)^{WMD}	<0.001
		Cross-sectional	-	-	-	-	-
	Matching	Non-matching	2	0.0	0.73	15.78 (7.61, 23.96)^{WMD}	<0.001
		Sex or age matching	1	-	0.00	104.49 (64.66, 144.32)^{WMD}	<0.001
DM (Yes vs. No)	Total		8	74.4	27.29	2.15 (1.41, 3.29)^{OR}	<0.001
	Type of control	Healthy controls	4	29.5	4.25	1.96 (1.41, 2.72)^{OR}	<0.001
		Hospital-based controls	4	86.9	22.98	2.54 (1.01, 6.43)^{OR}	0.049
	Type of stroke	All	-	-	-	-	-
		IS	7	77.5	26.72	2.24 (1.38, 3.66)^{OR}	0.001
		HS	1	-	0.00	1.69 (0.97, 2.94)^{OR}	0.066
	Study design	Cohort	2	25.6	1.34	2.29 (1.57, 3.35)^{OR}	<0.001
		Case-control	5	82.7	23.11	2.38 (1.14, 4.95)^{OR}	0.020
		Cross-sectional	1	-	0.00	1.23 (0.65, 2.32)^{OR}	0.518
	Matching	Non-matching	2	25.6	1.34	2.29 (1.57, 3.35)^{OR}	<0.001
		Sex or age matching	6	80.3	25.43	2.12 (1.14, 3.93)^{OR}	0.018
HTN (Yes vs. No)	Total		10	37.7	14.45	3.56 (3.00, 4.23)^{OR}	<0.001

Table 2. Continued

Variables			K*	I² (%)	Q test	Pooled ES (95% CI)	*P* Value
SBP (mmHg)	Total		3	0.0	0.27	13.42 (10.19, 16.64)^WMD	<0.001
DBP (mmHg)	Total		3	0.0	1.26	6.66 (4.61, 8.70)^WMD	<0.001
Triglycerides (mg/dL)	Total		8	60.9	17.88	21.48 (10.03, 32.94)^WMD	<0.001
	Type of control	Healthy controls	4	55.6	6.76	24.48 (10.15, 38.81)^WMD	0.001
		Hospital-based controls	4	69.6	9.88	18.23 (-1.68, 38.14)^WMD	0.073
	Type of stroke	All	-	-	-	-	-
		IS	8	60.9	17.88	21.48 (10.03, 32.94)^WMD	<0.001
		HS	-	-	-	-	-
	Study design	Cohort	2	0.0	0.29	10.85 (-5.77, 27.46)^WMD	0.201
		Case-control	5	73.1	14.86	23.99 (7.46, 40.51)^WMD	0.004
		Cross-sectional	1	-	0.00	24.20 (3.60, 44.80)^WMD	0.021
	Matching	Non-matching	3	0.0	1.27	16.11 (3.18, 29.04)^WMD	0.015
		Sex or age matching	5	73.1	14.86	23.99 (7.46, 40.51)^WMD	0.004
TC (mg/dL)	Total		6	86.9	30.06	15.08 (0.48, 29.68)^WMD	0.043
	Type of control	Healthy controls	3	93.9	32.67	18.79 (-9.57, 47.14)^WMD	0.194
		Hospital-based controls	3	46.8	3.76	11.92 (-0.06, 23.91)^WMD	0.051
	Type of stroke	All	-	-	-	-	-
		IS	6	86.9	30.06	15.08 (0.48, 29.68)^WMD	0.043
		HS	-	-	-	-	-
	Study design	Cohort	1	-	0.00	6.96 (-3.20, 17.12)^WMD	0.179
		Case-control	4	88.2	25.47	21.23 (2.16, 40.30)^WMD	0.029
		Cross-sectional	1	-	0.00	-2.80 (-21.29, 15.69)^WMD	0.767
	Matching	Non-matching	2	0.0	0.82	4.70 (-4.20, 13.60)^WMD	0.301
		Sex or age matching	4	88.2	25.47	21.23 (2.16, 40.30)^WMD	0.029
LDL-C (mg/dL)	Total		5	94.9	77.83	23.89 (0.93, 46.84)^WMD	0.041
	Type of control	Healthy controls	2	97.3	37.58	21.33 (-19.74, 62.40)^WMD	0.309
		Hospital-based controls	3	95.0	39.95	25.86 (-10.80, 62.51)^WMD	0.167
	Type of stroke	All	-	-	-	-	-
		IS	5	94.9	77.83	23.89 (0.93, 46.84)^WMD	0.041
		HS	-	-	-	-	-
	Study design	Cohort	1	-	0.00	0.41 (-8.75, 9.57)^WMD	0.930
		Case-control	3	78.8	9.43	41.30 (23.63, 58.93)^WMD	<0.001
		Cross-sectional	1	-	0.00	-2.10 (-12.38, 8.18)^WMD	0.689
	Matching	Non-matching	2	0.0	0.13	-0.70 (-7.54, 6.14)^WMD	0.841
		Sex or age matching	3	78.8	9.43	41.30 (23.63, 58.93)^WMD	<0.001
HDL-C (mg/dL)	Total		7	14.24	57.9	-2.31 (-4.30, -0.33)^WMD	0.023
	Type of control	Healthy controls	4	35.0	4.62	-0.79 (-2.42, 0.83)^WMD	0.337
		Hospital-based controls	3	0.0	1.21	-5.25 (-8.05, -2.45)^WMD	<0.001
	Type of stroke	All	-	-	-	-	-
		IS	7	14.24	57.9	-2.31 (-4.30, -0.33)^WMD	0.023
		HS	-	-	-	-	-
	Study design	Cohort	2	0.0	0.04	0.17 (-1.42, 1.75)^WMD	0.838
		Case-control	4	6.8	3.22	-2.77 (-4.67, -0.87)^WMD	0.004
		Cross-sectional	1	-	0.00	-6.90 (-11.59, -2.21)^WMD	0.004
	Matching	Non-matching	3	74.5	7.85	-1.51 (-4.75, 1.73)^WMD	0.362
		Sex or age matching	4	6.8	3.22	-2.77 (-4.67, -0.87)^WMD	0.004

* K, number of included studies; ES, effect size; IS, Ischemic stroke; HS, Hemorrhage stroke; OR, odds ratio; WMD, weighted mean differences; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total-cholesterol; LDL-c, Low-density lipoprotein-cholesterol; HDL-c, High-density lipoprotein-cholesterol; DM, diabetes mellitus; HTN, hypertension.

Table 3. Results of Sensitivity Analyses to Estimate the Effects of Each Study on Pooled ESs (WMD/OR)

Variables	Pre-sensitivity Analysis			Upper & Lower of ES	Post-sensitivity Analysis		
	No. of Studies Included	Pooled ESs	95% CI		Pooled ESs	95% CI	Excluded Studies
Mean age (year)	4	5.49	4.45, 6.54[WMD]	Upper	6.79	5.25, 8.33	Parizadeh et al[20]
				Lower	5.23	4.07, 6.39	Sarrafzadegan et al[27]
Sex (male vs. female)	6	1.23	0.85, 1.79[OR]	Upper	1.38	1.09, 1.76	Afshari et al[28]
				Lower	1.10	0.69, 1.76	Saneei et al[23]
Smoking (Yes vs. no)	10	1.44	1.02, 2.03[OR]	Upper	1.55	1.10, 2.21	Hesami et al[15]
				Lower	1.29	0.93, 1.79	Hamzehee-Moghadam et al[29]
BMI (kg/m²)	4	0.05	-1.41, 1.50[WMD]	Upper	0.70	-0.03, 1.43	Saneei et al[23]
				Lower	-0.43	-2.30, 1.43	Moshayedi et al[21]
WC (cm)	3	3.25	1.44, 5.06[WMD]	Upper	4.24	1.20, 7.27	Parizadeh et al[20]
				Lower	2.97	0.74, 5.21	Sarrafzadegan et al[27]
FBG (mg/dL)	3	36.86	7.66, 66.07[WMD]	Upper	60.08	-22.54, 142.70	Parizadeh et al[20]
				Lower	15.78	7.60, 23.95	Afshari et al[28]
DM (Yes vs. No)	8	2.15	1.41, 3.29[OR]	Upper	2.42	1.59, 3.67	Ashjazadeh et al[26]
				Lower	1.79	1.31, 2.46	Moshayedi et al[21]
HTN (Yes vs. No)	10	3.56	3.00, 4.23[OR]	Upper	3.95	3.27, 4.78	Parizadeh et al[20]
				Lower	3.30	2.74, 3.99	Saneei et al[23]
SBP (mm Hg)	3	13.42	10.19, 16.64[WMD]	Upper	14.07	10.01, 18.12	Parizadeh et al[20]
				Lower	13.04	9.07, 17.01	Sarrafzadegan et al[27]
DBP (mm Hg)	3	6.66	4.61, 8.70[WMD]	Upper	7.70	4.74, 10.66	Parizadeh et al[20]
				Lower	6.30	3.71, 8.89	Sarrafzadegan et al[27]
TG (mg/dL)	8	21.48	10.03, 32.94[WMD]	Upper	24.64	13.31, 35.97	Savadi-Oskouei et al[31]
				Lower	18.23	6.85, 29.62	Hosinian et al[16]
TC (mg/dL)	6	15.08	0.48, 29.68[WMD]	Upper	18.25	2.50, 33.99	Maghbooli et al[24]
				Lower	14.37	-5.22, 33.97	Savadi-Oskouei et al[31]
LDL-C (mg/dL)	5	23.89	0.93, 46.84[WMD]	Upper	30.58	4.02, 57.13	Maghbooli et al[24]
				Lower	15.54	-7.02, 38.10	Moshayedi et al[21]
HDL-C (mg/dL)	7	-2.31	-4.30, -0.33[WMD]	Upper	-1.50	-3.22, 0.22	Maghbooli et al[24]
				Lower	-3.06	-5.33, -0.78	Sarrafzadegan et al[27]

BMI, Body mass index; WC, Waist circumference; FB, Fasting blood glucose; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TG, triglycerides; TC, Total-cholesterol; LDL-C, Low-density lipoprotein-cholesterol; HDL-C, High-density lipoprotein-cholesterol; DM, Diabetes mellitus; HTN, Hypertension.

Discussion

Stroke risk stratification depends on various regional and ethnic factors that are taken into account as integral parts of resource assessment as well as bases for developing targeted stroke prevention programs. Currently, there is lack of related literature on the Iranian population regarding the risk factors of either ischemic or hemorrhagic strokes. Thus, the present comprehensive meta-analysis of observational studies on the Iranian population as an example of other LMICs was conducted to explore SRFs among Iranians. Overall, the included observational studies covered demographics (age and gender), traditional VRFs (HTN, DM, dyslipidemia, and family history of CVDs), and lifestyle factors (CS, OD, WC, and BMI). Notably, the majority of these predisposing factors were preventable. This study also provided essential information and a global insight into all modifiable and non-modifiable SRFs in the Iranian population and added to the information of all previous epidemiological studies in this field.[18,32-36] The meta-analysis findings also revealed that age, but not gender, was associated with the risk of stroke. HTN, SBP and DBP, DM, and FBG were accordingly correlated with increased risk of stroke among the traditional VRFs. Other

possible risk factors including CS, OD, and WC were further confirmed as independent stroke determinants in addition to high circulating levels of TG, LDL-C, TC, and low HDL-C.

Demographics Factors

In this regard, a significant association was observed for mean age, whereas gender did not influence the risk of stroke. Stroke distribution was also correlated with age and gender.[37] The highlighted impact of aging was in line with a previous systematic study from Iran,[17] underlining a slight predominance for females in older age in contrast to a small prevalence for males in younger age.[17] It should be noted that a large cohort study from northwestern Iran had reported a similar incidence in women and men.[38] Nevertheless, in subgroup analyses, male gender was found to be significantly associated with stroke. However, these findings should be cautiously explored and further studies are needed to evaluate the rate of age-specific stroke in Iran because the number of articles in age-matched groups is not sufficient (only one study was age-matched for gender while five studies were not). Considering the fact that several studies from Middle Eastern countries such as Iraq,

Table 4. The Findings of Quality Assessment Using the Newcastle-Ottawa Scale

Author Name	Study design	Selection	Comparability	Exposure/Outcome	Overall Quality Assessment Score
Fahimfar et al[14]	Cohort sttudy	****	*	**	7
Saneei et al[23]	Case-control study	**	**	**	6
Moshayedi et al[21]	Case-control study	***	*	**	6
Maghbooli et al[24]	Cross-sectional study	***	**	**	7
Sadreddini et al[25]	Case-control study	***	*	***	7
Parizadeh et al[20]	Cohort Study	***	**	***	8
Hosinian et al[16]	Case-control study	**	*	**	5
Ashjazadeh et al[26]	Case-control study	**	*	***	6
Hesami et al[15]	Case-control study	**	*	**	5
Sarrafzadegan et al[27]	Cohort study	****	*	**	7
Saberi et al[22]	Cross-sectional study	**	*	*	4
Afshari et al[28]	Case-control study	***	**	**	7
Hamzehee-Moghadam et al[29]	Case-control study	**	*	***	6
Savadi-Oskouei et al[30]	Case-control study	*	*	**	4
Savadi-Oskouei et al[31]	Case-control study	*	*	**	4

* For case-control studies, there are four items within the selection: 1) indicates cases adequately defined; 2) representativeness of the series of cases; 3) community controls; 4) controls have a group of stroke-free population), one item (with two sub-items A and B) within the comparability: A study controls for important factor and B study controls for additional factor(s), and three items within the exposure: 1) ascertainment of exposure by records; 2) same method of ascertainment used for cases and controls; and 3) same non-response rate for both groups. For cohort studies are four items within the selection: 1) shows exposed cohort truly representative in the studied community; 2) non-exposed cohort drawn from the same community as the exposed cohort; 3) ascertainment of exposure by records; 4) outcome of interest was not present at start of study, one item (with two sub-items A and B) within the comparability: A cohorts comparable on the basis of important factor and B cohorts comparable for any additional factor, and three items within the outcome: 1) assessment of outcome by record linkage or independent blinding; 2), follow-up long enough for outcomes to occur; and 3) follow up adequacy of cohorts. For cross-sectional studies are three items within the selection: 1) shows samples truly representative; 2) same characteristics between respondents and non-respondents and enough response rate; 3) exposure ascertainment by validated measurement tool, one item (with two sub-items A and B) within the comparability: A study controls for important factor and B study controls for additional factor, and two items within the outcome: 1) assessment of outcome by record linkage or independent blinding; 2) the statistical test is clearly described and appropriately presented.

Saudi Arabia, and Palestine have shown significant female predominance,[39] determining gender-related predisposing factors requires in-depth investigations to shed light on the causes of this discrepancy between Iran and other nations in the Middle East.

Traditional VRFs

To examine the metabolic profile of the patients, the crucial role of diet should be taken into account. Diet can be thus involved in numerous interconnected mechanisms underlying stroke and related to balance in blood pressure, blood lipids, thrombosis and coagulation, oxidative stress, systemic inflammation (SI), endothelial function, glucose/insulin homeostasis, gut microbiome, and body weight.[40] HTN, DM, and dyslipidemia (including high levels of TG, TC, LDL-C, and low levels of HDL-C), as three comorbidities that could very often co-exist in patients, were thus regarded as SRFs in this study. It seems that these populations are susceptible to higher TG and lower HDL-C levels. Nevertheless, after additional analysis based on gender and age matching, the findings revealed that TC and LDL-C levels were also significantly associated as SRFs. A meta-analysis by Wang et al further concluded that a higher level of HDL-C was correlated with a lower risk of hemorrhagic stroke.[41] Of note, overall dyslipidemia is one of the important risk factors for coronary artery diseases (CADs) and stroke, which can be affected and changed

by lifestyle, diet, and medications.[42] In this respect, recent studies have suggested that inadequate physical activity is correlated with decreased HDL-C and increased TG levels.[43,44] Also, HTN and DM have been repeatedly among the strongest SRFs.[45-47] DM also augments the risk of stroke by four times.[48] The INTERSTROKE study had similarly listed HTN and DM among the ten factors accounting for over 90% of SRFs,[10] which is consistent with the results of a nationwide German study focusing on stroke onset below 55 years of age. In that study, HTN, dyslipidemia, and DM were mentioned among the top eight risk factors and the similarity with attributed risks in the older population was emphasized.[49] A meta-analysis of the Chinese population correspondingly underlined the significance of HTN and DM as leading SRFs while hyperlipidemia was mildly correlated.[47] A review of the Middle East studies on stroke patients further revealed that the prevalence rate of HTN was 62.1% followed by dyslipidemia with 36.8% and DM with 33.1%.[18] Although many risk factors are common across demographic groups, a universal weight cannot be applied due to variations in importance and prevalence of the given factors.[10,47] Thus, screening and prevention should be designated based on local priorities. However, a holistic approach is crucial as risk factors are often intertwined. Furthermore, LMICs should assess what part of resources, i.e., human resources, healthcare facilities, diagnostic and laboratory

services, medications, and access to transportation, is more important to be improved with regard to stroke care.[50]

In this study, family history of CVDs was not significantly correlated with stroke in the Iranian population. This might be due to the limitation in the included studies that had been considered suitable for evaluating the relationship between family history and stroke. It should be noted that family history is a well-established SRF[51] especially at a younger age.[33,52] In this respect, a national cohort study in the United States showed that a positive family history of stroke was associated with physiological and behavioral factors such as HTN and CS, implying that family history could be also partially attributed to modifiable factors.[53] Unfortunately, the presence of such an association could not be assessed based on the existing data in this study. Accordingly, encouraging family members of stroke patients to pursue a stricter healthy lifestyle and to adhere to routine monitoring seems very reasonable principally in LMICs, wherein prevention should be highly prioritized due to limited resources.

Lifestyle Factors

Extensive research has revealed the role of CS in stroke.[10,46,49] A meta-analysis covering studies for almost 50 years on approximately four million individuals also confirmed CS as an independent SRF with a similar risk in both men and women, confirming that both genders could benefit from CS cessation.[54] Moreover, non-smokers, especially women, could be subject to a greater risk of stroke, ischemic heart disease, and chronic obstructive pulmonary disease (COPD) subsequent to second-hand smoke exposure.[55] Accordingly, Austin et al[56] suggested that the link between COPD and stroke was not only correlated with shared traditional risk factors including aging and smoking, but also the COPD-related SI and oxidative stress that could aggravate cerebral vascular dysfunction and platelet hyperactivity.

Regarding dependence, most studies have focused on alcohol abuse, while it is less prevalent in Iran and very likely to be underreported in surveys due to its illegality. As a result, no assumptions could be offered on alcohol. On the other hand, OD is a more common public health concern in Iran. It is noteworthy that substance abuse is illegal in Iran and it is socially stigmatized. Therefore, the possibility of underreporting cannot be ignored. The findings revealed that total OD (regardless of its type) was a SRF. Several studies on the Iranian population have also confirmed OD as a risk factor for stroke and CVDs,[13,57-59] possibly by enhancing plasma fibrinogen activity and chance of atherosclerosis.[59]

The impact of obesity and BMI on development of stroke has been similarly supported in large-scale studies.[49] A meta-analysis by Guo et al[60] concluded that young adults with overweight or obesity were prone to an elevated risk of stroke probably independent of other

cardioVRFs. A meta-analysis of prospective studies with two million participants by Strazzullo et al further found that overweight and obesity were linked with increased risk of ischemic stroke, at least in part, independently from lifestyle, age, and other VRFs.[61] The findings of the present study were in favor of the adverse impact of WC on stroke but not BMI. Interestingly, it has been demonstrated that by excluding the effect of BMI, abdominal obesity *per se*, in terms of WC and waist-to-height ratio, turns out to be a common risk factor in both genders.[62] Further studies are thus needed to assess the role of WC as a SRF in comparison with other anthropometric factors such as BMI. Unfortunately, the infrastructure to facilitate physical activity is rather underdeveloped in LMICs like Iran, even though the costs can outweigh the damage from diseases related to excess weight and sedentary life.

Strengths and Limitations

The present study was the first attempt as the most comprehensive systematic review and meta-analysis to determine SRF in the Iranian population. However, there were several limitations. Firstly, the number of studies evaluated for risk factors affecting stroke in the Iranian population was small. Secondly, some articles were excluded due to their methodological limitations. Thirdly, there was heterogeneity among the included primary studies regarding their outcomes. Fourthly, the subgroup analysis did not adjust for confounding variables. Therefore, the results are possibly affected by confounding factors and should be interpreted with caution. Accordingly, the relationship between each risk factor and stroke was estimated based on a comparison of the distribution of risk factors between case and control groups (univariate analysis) because the studies with the adjusted findings were not adequate.

Conclusion

Apparently, stroke seems to be strongly associated with lifestyle and environmental age-related factors in Iran. Among the risk factors mentioned, HTN, SBP and DBP, DM, and FBG were related to increased risk of stroke among traditional VRFs. Other possible risk factors including CS, OD, and WC were further established as independent stroke determinants as well as high circulating levels of TG, LDL-C, TC, and low HDL-C. Considering recent lifestyle alterations in the Iranian society, stroke continues to take its toll on a more extensive scale, especially with a shift towards the younger population if prompt public awareness and strict preventive policies remain neglected.

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